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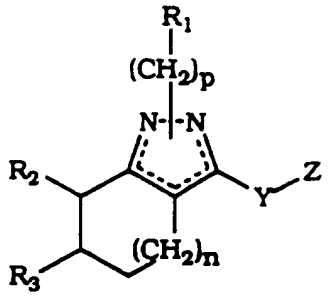
(54) Tetrahydroindazole, tetrahydrocyclopentapyrazole, and hexahydrocycloheptapyrazole compounds and their use as HMG-CoA reductase inhibitors.

(57) Compounds of the general formula I :



are disclosed as useful in the treatment or prevention of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis. Novel intermediate compounds used to make the compound of formula I are also disclosed.

EP 0 529 854 A2

BACKGROUND OF THE INVENTION

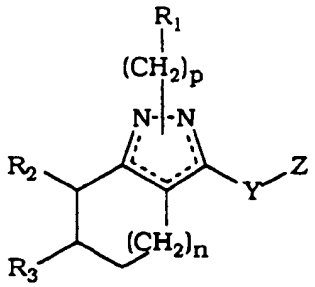
Compounds which inhibit HMG-CoA reductase, the enzyme controlling the rate-limiting step in cholesterol biosynthesis, are assuming an important role in the management of certain forms of hyperlipidemia. Lovastatin, disclosed in U. S. Patent 4,231,938, has been approved for use in the treatment of primary hypercholesterolemia, a disease characterized by normal serum triglyceride levels and elevated serum levels of low density lipoprotein (LDL) cholesterol and total cholesterol. In several large clinical studies, lovastatin was found to decrease plasma LDL and total cholesterol concentrations 25% to 40% while causing small but significant increases (up to 10%) in high density lipoprotein (HDL) cholesterol concentration. When compared with cholestyramine and probucol, two drugs used in the treatment of primary hypercholesterolemia, lovastatin reduced LDL cholesterol levels to a significantly greater extent. In addition, combined administration of lovastatin with other hypolipidemic agents was found to potentiate their effects on LDL and total cholesterol concentrations.

The biochemical target for lovastatin is HMG-CoA reductase, the enzyme which catalyzes the reduction of HMG-CoA to mevalonic acid. Lovastatin, in its open dihydroxy acid form, is a reversible, competitive inhibitor of the enzyme. A number of compounds structurally related to lovastatin have been shown to be inhibitors of HMG-CoA reductase. These include simvastatin (U.S. Patent No. 4,444,784 and related compounds disclosed in U.S. Patent No. 4,444,784). Sankyo has reported a related compound, pravastatin (U.S. Patent No. 4,346,227). Sandoz has reported a number of HMG-CoA reductase inhibitors: indoles (U. S. Patent No. 4,739,073), pyrazoles (U.S. Patent No. 4,613,610), imidazoles (U.S. Patent No. 4,808,607), and pyrazolopyridines (U.S. Patent No. 4,822,799). Merck disclosed biphenyl-containing inhibitors in U.S. Patent No. 4,375,475. Hoechst AG disclosed non-heterocyclic HMG-CoA reductase inhibitors in Tetrahedron Letters, 1988 29, 929. Bristol-Myers reported tetrazole-containing compounds in UK Patent 2,202,846. Acylpyrroles are reported in U. S. Patent No. 4,681,893 by Warner-Lambert. Warner-Lambert also disclosed pyrimidines in U.S. Patent No. 4,868,185 and quinolines in U.S. Patent No. 4,761,419. Bayer AG reported tri-arylpyrroles in European Patent 287,890. Rorer reported aryl-cycloalkene and aryl-cycloalkadiene inhibitors in U.S. Patent Nos. 4,892,884 and 4,900,754. Squibb reported a number of potent compounds based on a variety of heterocycles in Journal of Medicinal Chemistry, 1990 33, 2852. Finally, Upjohn disclosed in WO 867,357 an anti-inflammatory, anti-allergic compound generically described as cyclopentapyrazole.

The compounds of the present invention are structurally different from the known compounds and have been shown to be potent inhibitors of HMG-CoA reductase and cholesterol biosynthesis.

SUMMARY OF THE INVENTION

Novel tetrahydroindazole, tetrahydrocyclopentapyrazole, and hexahydrocycloheptapyrazole compounds of the general formula I:

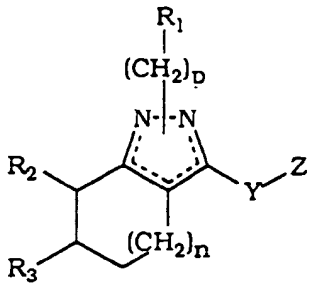


I

wherein R_1, R_2, R_3, Y, Z, n, and p are defined hereinafter have been found to be potent compounds for inhibiting HMG-CoA reductase and cholesterol biosynthesis and are thus useful in the treatment or prevention of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the following general formula I:



I

R_1 is selected from any one of H, C_1-C_8 alkyl, aryl, or substituted aryl. The R_1 substituent may be attached either directly or indirectly to either of the ring nitrogens but not both at the same time. Two double bonds represented by the dotted line in the nitrogen containing ring are positioned accordingly depending upon the position of the R_1 substituent. Examples of suitable R_1 substituents include 4-fluorophenyl and 4-chlorophenyl.

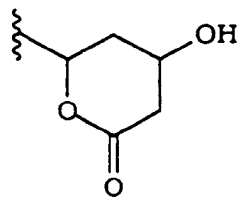
R_2 is selected from any one of H, C_1-C_8 alkyl, aryl, substituted aryl, aralkyl wherein the alkyl portion is C_1-C_4, substituted aralkyl wherein the alkyl portion is C_1-C_4, aralkenyl wherein the alkenyl portion is C_1-C_4, or C_3-C_8 cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and the like. Examples of suitable R_2 groups include H, 4-fluorobenzyl, 3-phenyl-2-propenyl, cyclohexyl, ethyl, methyl, 1-naphtylmethyl, 2-naphthylmethyl, 4-phenylbenzyl, benzyl, 4-chlorobenzyl, 4-isopropylbenzyl, 4-methoxybenzyl and 4-t-butylbenzyl.

R_3 is H.

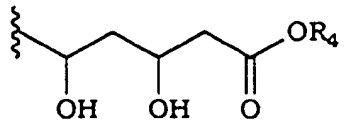
R_2 and R_3 may be taken together to form a benzo or naphtho ring system.

Y is C_1-C_8 alkyl or C_1-C_8 alkenyl such as CH=CH and $CH=C(CH_3)$.

Z is selected from any one of:



II

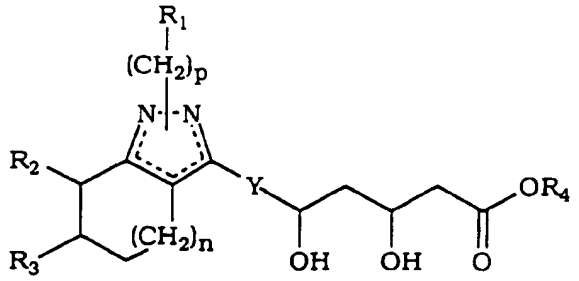


III

wherein R_4 is H, C_1-C_8 alkyl, a protonated amine of the formula $HN(R_5)_3^+$ wherein R_5 is H or C_1-C_8 alkyl, or a cation such as Na^+, K^+, Li^+, Ca^{2+}, or Mg^{2+}.

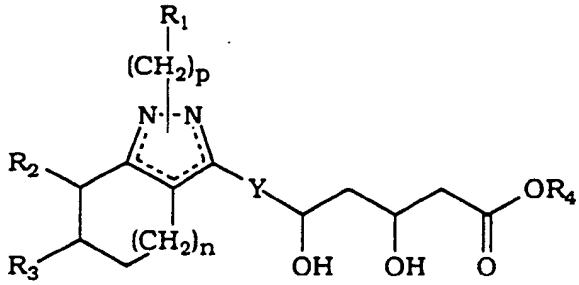
The values for n are 0 to 3 and the values for p are 0 to 3.

The compounds of formula I can be generally represented by three sub-groups of compounds represented by formulas **I(a)**, **I(b)**, and **I(c)** which are set forth as follows:



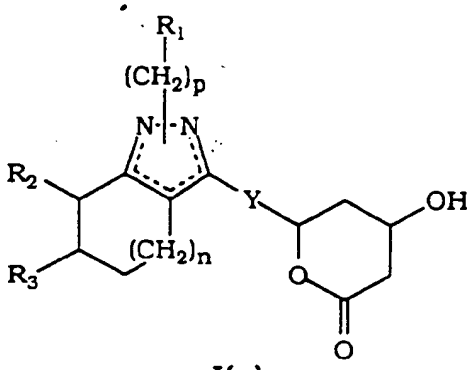
I(a)

wherein R_4 is any of C_1-C_8 alkyl, and R_1, R_2, R_3, Y, n, and p are as defined above; or



I(b)

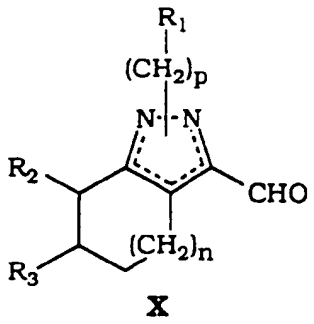
wherein R_4 is H, a cation such as Na^+, K^+, Li^+, or a protonated amine of the formula $HN(R_5)_3^+$, wherein R_5 is H or C_1-C_8 alkyl, and R_1, R_2, R_3, Y, n, and p are as defined above; or



I(c)

wherein R_1, R_2, R_3, Y, n, and p are as defined above.

Also within the scope of this invention are intermediate compounds which are useful in making the compounds of formula I. The intermediate compounds are represented by the general formula X:



X

wherein R_1, n, and p are as defined above.

R_2 is selected from any one of H, C_1-C_8 alkyl, aryl, substituted aryl, aralkyl wherein the alkyl portion is C_1-C_4, substituted aralkyl wherein the alkyl portion is C_1-C_4, aralkenyl wherein the alkenyl portion is C_1-C_4, or C_3-C_8 cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and the like.

R_3 is H.

R_2 and R_3 may be taken together to form a benzo or naphtho ring system.

The term "aryl," as used herein alone or in combination with other terms, indicates aromatic hydrocarbon groups such as a phenyl or naphthyl group. The term "aralkyl" indicates a radical containing a lower C_1-C_8 alkyl group substituted with an aryl radical or substituted aryl radical as defined above.

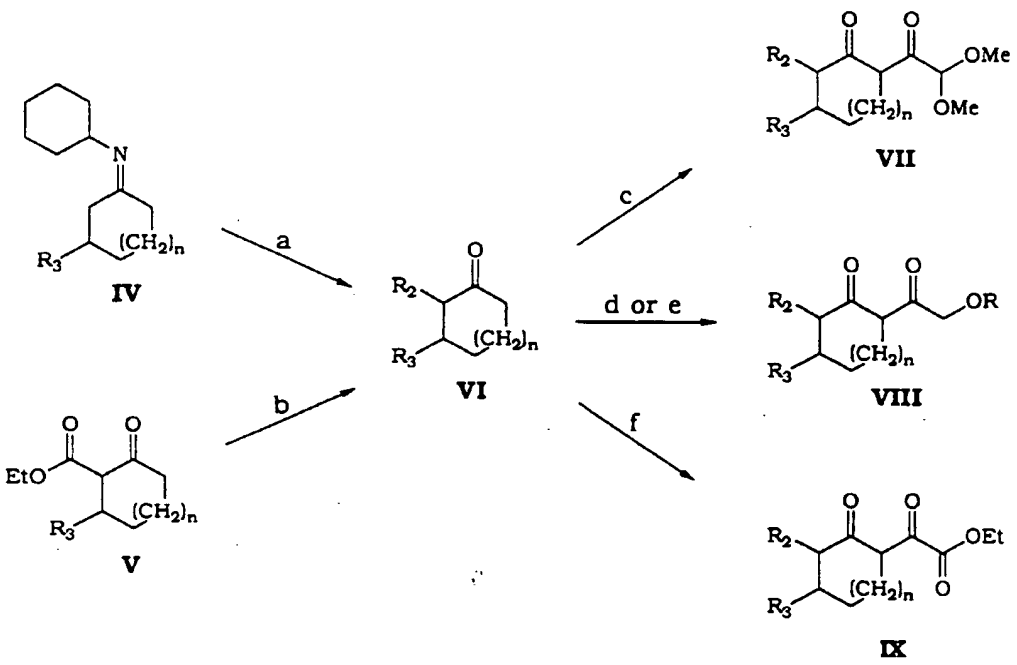
The aryl groups and the ring formed by R_2 and R_3 may be independently substituted with any of C_1-C_8 alkyl, such as methyl, ethyl, propyl, isopropyl, t-butyl, and sec-butyl; alkoxy such as methoxy and t-butoxy; halo such as fluoro, chloro, bromo, and iodo; or nitro.

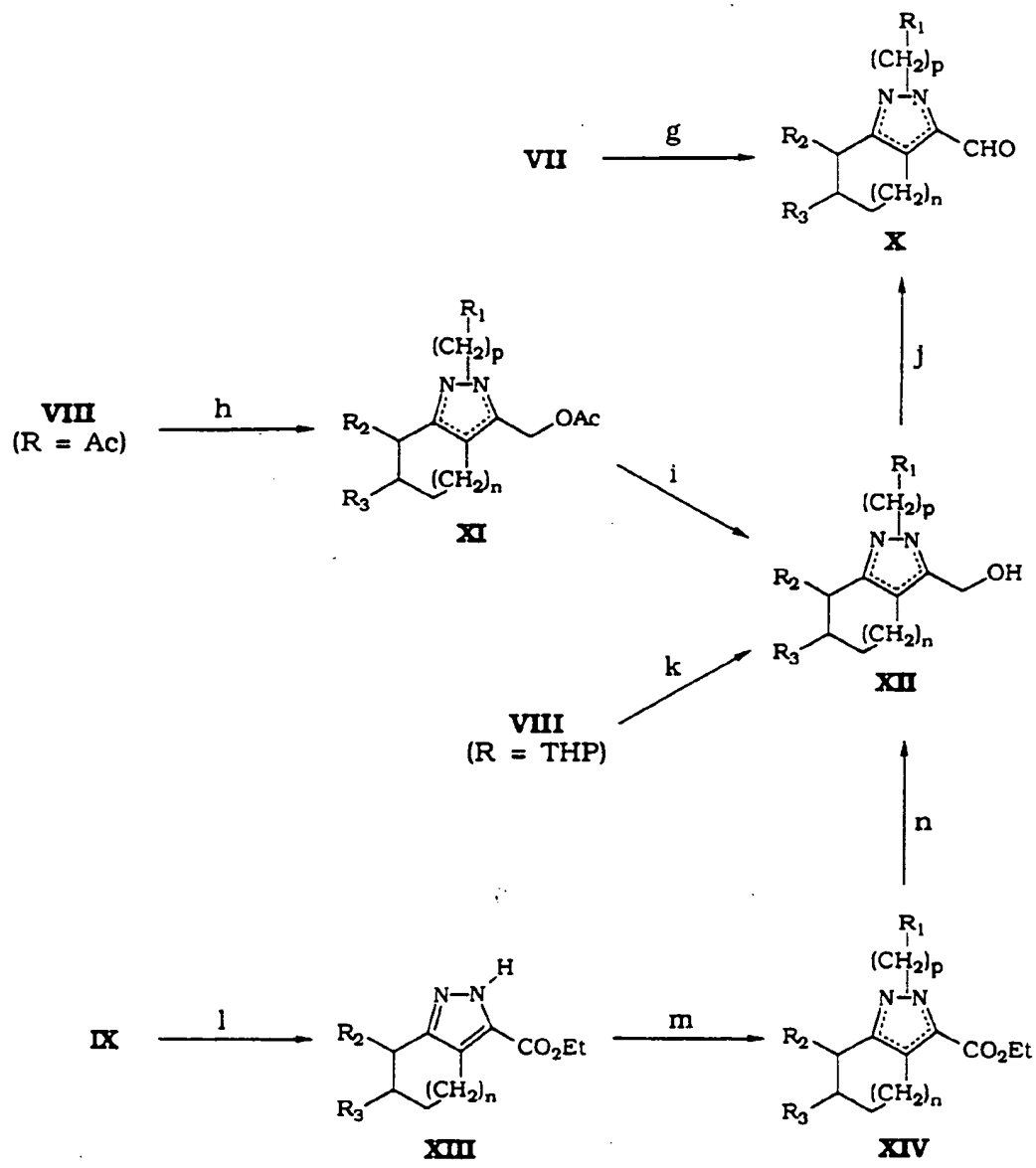
As used herein alkyl and alkoxy include straight and branched chains. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl , neopentyl, n-hexyl, 1-methylpentyl, 3-methylpentyl. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. The term "independently" is used with respect to aryl and ring substituents to indicate that when more than one of such substituents is possible such substituents may be the same or different from each other. Position 1 in the N-containing ring is the N atom adjacent to the ring fusion.

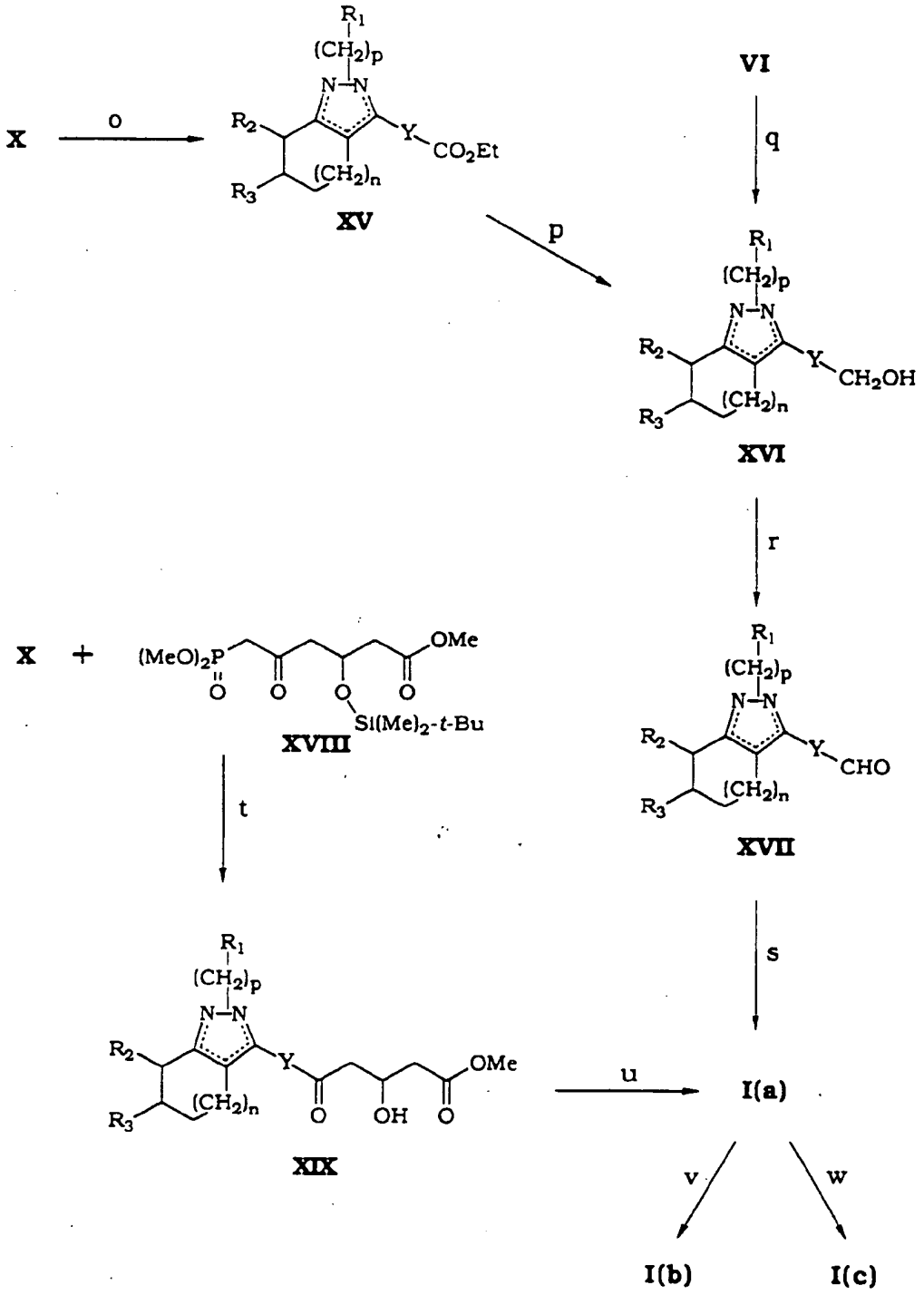
The compounds produced according to the invention include the various individual isomers as well as the racemates thereof, e.g. the isomers arising from the various attachments on the side chain Z as well as the substituents R_2 and R_3.

The compounds of formula I and intermediates of formula X may be prepared according to the following general reaction scheme, which as is apparent contains a plurality of alternative routes depending upon starting materials and the reactions carried out.

Reaction Scheme




VII
g
X
VIII
(R = Ac)
h
XI
i
j
XII
VIII
(R = THP)
k
n
IX
l
XIII
m
XIV



If desired, the substituted cyclic ketone **VI** may be obtained from commercial suppliers (Aldrich Chemical Co., Lancaster Synthesis Ltd., or Wiley Organics). Alternatively, compound **VI** may be prepared as shown in the reaction scheme by treatment of imine **IV** (Stork, G., Dowd, S. R. J. Am. Chem. Soc. 1963 85, 2178-80) in an inert solvent such as THF with an appropriate base such as s-BuLi or LiN(*i*-Pr)$_2$ (LDA) at -78 to 0°C for

15 to 45 min under N_2, followed by alkylation at 0°C to RT (room temperature) for 16 h, followed by hydrolysis of the resulting imine with 2N HCl at RT for 5 h. Alternatively, compound **VI** may be prepared by treatment of the 2-carboethoxy cyclic ketone **V** (commercially available from Aldrich Chemical Co.) in an inert solvent such as benzene or DMF with an appropriate base such as NaH at 0 to 25 °C for 30 to 60 min under N_2, followed by alkylation at 0°C to RT for 2 to 3 days, followed by hydrolysis of the ester and decarboxylation of the resulting acid with 6N HCl at reflux for 2 to 3 days.

Compound **VI** can be treated with an appropriate base, such as LDA or $LiN(SiMe_3)_2$, in an inert solvent, such as THF, at -78°C to 0°C and acylated with methyl dimethoxyacetate at 0°C to RT for 16 h to give the diketone **VII**. Compound **VII** is dissolved in an appropriate solvent, such as EtOH, and treated with a substituted hydrazine for 16 h at RT. The resulting acetal is hydrolyzed with 1N HCl at reflux to give the aldehyde **X** as a separable mixture of regioisomers.

Compound **X** can also be prepared from composed **VI** by several alternate routes. Thus, compound **VI** is treated with pyrrolidine and acetoxyacetyl chloride to give the acetoxy methyl diketone **VIII** (R = Ac: Dolmazon, R. J. Heterocyclic Chem., 1982, 19, 117-121). Reaction of **VIII** with a substituted hydrazine in a suitable solvent, such as EtOH, from RT to reflux for 4 to 10 h gives the regioisomeric mixture of acetoxy compounds **XI**, which is dissolved in an alcoholic solvent such as MeOH and hydrolyzed with 1N NaOH at RT to provide the separable mixture of alcohols **XII**. Alternatively, the THP derivative of compound **VIII** (R = THP), prepared by the treatment of compound **VI** and ethyl (tetrahydropyranyloxy)acetate (Ireland, R. Tetrahedron Lett., 1989, 30, 919-922) in ether with a suitable base, such as NaH or NaOEt, from 0°C to RT for 16 h, can be treated with a substituted hydrazine at reflux for 4 h, followed by hydrolysis of the THP group with 1N HCl to give the separable mixture of alcohols **XII**.

Alternatively, compound **VI** is treated with NaH and diethyl oxalate to give the 2-substituted dioxoacetate **IX** (Tsuboi, S. J. Org. Chem, 1987, 52, 1359-62). Treatment of compound **IX** in MeOH with hydrazine hydrate at RT to 60°C for 16 h gives the 3-carboethoxy compound **XIII**. The separable regioisomeric mixture of esters **XIV** is prepared by treating compound **XIII** with a suitable base, such as NaH, in an inert solvent, such as DMF, at 140°C for 15 min under N_2, followed by the addition of the alkylating agent at 140°C. The alcohol **XII** is prepared by reduction of the corresponding 3-carboxylate **XIV** with a suitable reducing agent, such as $LiAlH_4$, in an inert solvent, such as THF, at 0°C to RT for 2 to 3 h under N_2. Oxidation of compound **XII** with either MnO_2 in an appropriate solvent, such as benzene, or pyridinium chlorochromate in an appropriate solvent, such as methylene chloride, gives the corresponding aldehyde **X**.

Treatment of compound **X** with NaH and triethyl phosphonoacetate or triethyl phosphonopropionate in an inert solvent such as THF at 0° to RT for 16 h gives the corresponding ester **XV**. Reduction of the ester is accomplished by treatment of **XV** with $(i\text{-}Bu)_2AlH$ in an inert solvent, such as toluene or THF, for 1 to 2 h at 0°C under N_2 to give the alcohol **XVI**. Alternatively, compound **XVI** can be prepared from the appropriately substituted cyclic ketone **VI** by treatment of said ketone with a substituted hydrazine and an appropriate base, such as NaOAc, in EtOH at reflux for 3 h to give the hydrazone. The hydrazone is then treated with a suitable base, such as LDA, at -10°C and acylated with methyl 4-tetrahydropyranyloxy-2-butenoate (Harnish, W.; Morera, E.; Ortar, G. J. Org. Chem., 1985, 50, 1990-2); the resulting intermediate is treated with 3N HCl at reflux for 15 min, followed by reaction with pyridinium p-toluenesulfonate at reflux for 8 h under N_2 to give the substituted alcohol **XVI**. Oxidation of alcohol **XVI** by treatment with MnO_2 in an appropriate solvent, such as benzene, at reflux for 3 h or with CrO_3 and pyridine in an appropriate solvent, such as methylene chloride, gives aldehyde **XVII**. Ethyl acetoacetate is treated with an appropriate base, such as LDA, or mixture of bases, such as NaH and n-BuLi , and reacted with compound **XVII** at 0 to -10°C for 1 to 2 h in an inert solvent such as THF. Reaction of the intermediate ester with Et_3B in a solvent mixture such as 1:4 MeOH:THF at 0°C, followed by treatment with $NaBH_4$ at -78°C to RT for 16 h, gives the dihydroxyheptenoate **I(a)**.

Alternatively, compound **I(a)** can be prepared by the reaction of compound **X** with methyl 3-[(t-butyldimethylsilyl)oxy-6-(dimethoxyphosphinyl)-5-oxohexanoate **XVIII** (Theisen, P. D.; Heathcock, C. H. J. Org. Chem., 1988, 53, 2374-81), LiCl, and DBU in an appropriate solvent, such as acetonitrile, at RT under N_2 for 6 h to give 3-hydroxy-5-oxoheptenoate **XIX**. Treatment of ester **XIX** with Et_3B in a solvent mixture such as 1:4 MeOH:THF at 0 to -78°C, followed by reaction with $NaBH_4$ at -78°C to RT for 16 h gives the dihydroxyheptenoate **I(a)**. Compound **I(a)** can be hydrolyzed with aqueous NaOH or KOH and a suitable alcoholic solvent, followed optionally by neutralization with dilute aqueous HCl and treatment with an amine base, to give the dihydroxyheptenoic acid derivative **I(b)**. Hydrolysis of compound **I(a)** as described above to the crude acid, followed by treatment of said acid with an appropriate carbodiimide, such as 1-cyclohexyl-3-(2-morpholinoethyl) carbodiimide metho-p-toluenesulfonate, in an inert solvent, such as methylene chloride, at 0°C to RT for 16 h, gives the tetrahydropyranyl compound **I(c)**.

The compounds of this invention are useful as hypocholesterolimic or hypolipidemic agents by virtue of their abiity to inhibit the biosynthesis of cholesterol through the inhibition of the enzyme 3-hydroxy-3-methyl-

glutaryl coenzyme A reductase (HMG-CoA reductase). The ability of the compounds of the present invention to inhibit the biosynthesis of cholesterol was measured by two different tests.

HMG-CoA Reductase Isolation And Assay

Livers were harvested from male Wistar rats (250 g) following a five day feeding with powdered chow containing 2% cholestyramine. Ammonium sulfate precipitated HMG-CoA reductase was prepared from these livers according to the method of Heller, et. al. (Heller, R. A., Shrewsbury, M.A. Journal of Biological Chemistry, 251, 1976, 3815-3822). HMG-CoA reductase activity was measured using a modification of the procedure of Edwards, et. al . (Edwards, P. A., Lemongello, D., Fogelman A. M. Journal of Lipid Research, 20, 1979, 40-46). The effects of compounds on HMG-CoA reductase activity were determined by combining the compound with the enzyme and preincubating for 10 minutes prior to addition of the substrate HMG-CoA reductase.

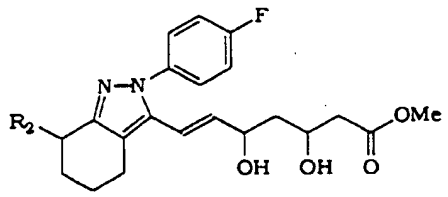
Cell Culture Cholesterol Biosynthesis Assay

Hep-G2 cells obtained from the American Type Culture Collection were maintained in MEM (minimal essential medium) obtained from GIBCO containing Earles salts and supplemented with 10% HI-FBS. For cholesterol biosynthesis experiments, cells were plated into T25 flasks. When the cells were 2/3 confluent, they were fed MEM containing Earles salts and delipidated serum protein (DLP) at 5mg/mL and then incubated for a period of 24 h. DLP was prepared according to the procedure of Rothblat, et. al. (Rothblat, G. H., Arrbogast, L.Y., Ouellette, L., Howard, B.V. In Vitro (Rockville), 12, 1976, 554-557). The DLP medium was then removed and 3.3 mL of media containing the drug indicated was added. Monolayers were incubated with drug for 2.5 h at which time ^{14}C-acetate (0. 2 mCi/ 12 mmol) was added and cells incubated for an additional 3 h. The reaction was stopped by the addition of 0.2 mL of 12 N H_2SO_4; ^{3}H-cholesterol and ^{3}H-oleic acid were added as internal recovery standards, and samples were saponified. Fatty acids were extracted and digitonin precipitable sterols were recovered according the procedure of Kanduch and Saucier (Kandutch, A. A., Saucier, S. E. Journal of Biological Chemistry, 244, 1969, 2299-2305). To adjust for cell number per flask, the cholesterol synthesized was normalized to the fatty acids synthesized and results were expressed as percent inhibition vs. control.

The activities of certain representative examples are shown in Tables I-V. In the Tables, Me means methyl, Et is ethyl, Pr is propyl, Bu is butyl, c-Hex is cyclohexyl, Ph is phenyl, Nap is naphthyl, MeO is methoxy, and Biphenyl is (1,1'-biphenyl)-4-yl. Each of the compounds was tested in the form of a racemic mixture.

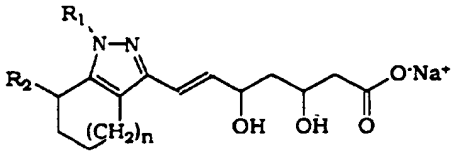
Each of the compounds in Tables I-V was tested in one or both of the biological assays. The symbol "nt" indicates that a particular compound was not tested.

Table I



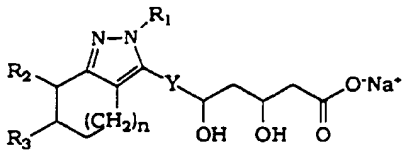
Compound Number	R_2	Cell Culture Cholesterol Biosynthesis IC_{50} (μM)
42	(2-Nap)-CH_2	0.365
43	(4-i-Pr-Ph)-CH_2	0.12

Table II



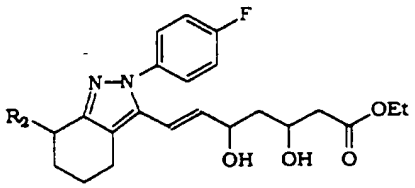
Compound Number	n	R_1	R_2	HMG-CoA Reductase IC_{50} (nM)	Cell Culture Cholesterol Biosynthesis IC_{50} (μM)
2	0	4-F-Ph	H	100,000	nt
3	1	4-F-Ph	(4-F-Ph)-CH_2	31,000	27
4	1	4-F-Ph	c-Hex	47,000	nt
5	1	4-F-Ph	Et	35,000	nt
6	1	4-F-Ph	Me	100,000	nt
7	1	4-F-Ph	Ph-$(CH_2)_2$	nt	>10
8	1	4-F-Ph	Ph-CH=CH-CH_2	3,000	nt
9	2	(4-F-Ph)-CH2	H	100,000	nt

Table III



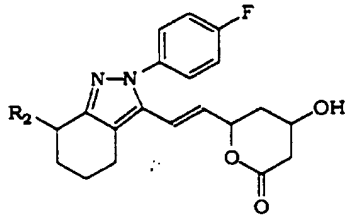
Compound Number	n	R_1	R_2	R_3	Y	HMG-CoA Reductase IC_{50} (nM)	Cell Culture Cholesterol Biosynthesis IC_{50} (μM)
1	1	4-F-Ph	(Biphenyl)-CH_2	H	CH=CH	2.7	0.24
10	0	4-F-Ph	H	H	CH=CH	5,100	nt
11	1	4-F-Ph	(1-Nap)-CH_2	H	CH=CH	26	0.37
12	1	4-F-Ph	(2-Cl-Ph)-CH_2	H	CH=CH	100	1.3
13	1	4-F-Ph	(2-Nap)-CH_2	H	CH=CH	5.6	0.33
14	1	4-F-Ph	(3-MeO-Ph)-CH_2	H	CH=CH	48	1.09
15	1	4-F-Ph	(3,4-di-MeO-Ph)-CH_2	H	CH=CH	168	3.9
16	1	4-F-Ph	(4-Cl-Ph)-CH_2	H	CH=CH	58	0.36
17	1	4-F-Ph	(4-F-Ph)-CH_2	H	CH=CH	150	0.70
18	1	4-F-Ph	(4-i-Pr-Ph)-CH_2	H	CH=CH	14	0.26
19	1	4-F-Ph	(4-Me-Ph)-CH_2	H	CH=CH	19	0.13
20	1	4-F-Ph	(4-MeO-Ph)-CH_2	H	CH=CH	14	0.46
21	1	4-F-Ph	(4-t-Bu-Ph)-CH_2	H	CH=CH	16	0.135
22	1	4-F-Ph	------6,7-Benzo------		CH=CH	13,000	nt
23	1	4-F-Ph	c-Hex	H	CH=CH	7,700	nt
24	1	4-F-Ph	Et	H	CH=CH	1,000	nt
25	1	4-F-Ph	H	H	CH=CH	2,500	nt
26	1	4-Cl-Ph	H	H	CH=CH	8,800	nt
27	1	4-F-Ph	H	H	CH=C(Me)	2,700	nt
28	1	4-F-Ph	Me	H	CH=CH	1,100	nt
29	1	4-F-Ph	n-Pr	H	CH=CH	1,300	nt
30	1	4-F-Ph	Ph	H	CH=CH	3,100	nt
31	1	4-F-Ph	Ph-CH_2	H	CH=CH	85	0.22
32	1	4-F-Ph	Ph-$(CH_2)_2$	H	CH=CH	334	1.75
33	1	4-F-Ph	Ph-$(CH_2)_3$	H	CH=CH	160	1.1
34	1	4-F-Ph	Ph-CH=CH-CH_2	H	CH=CH	32	1.3
35	1	4-F-Ph	s-Bu	H	CH=CH	1,000	nt
36	2	4-F-Ph	------7,8-Benzo------		CH=CH	2,100	nt
37	2	4-F-Ph	H	H	CH=CH	3,800	nt
38	2	(4-F-Ph)-CH_2)	H	H	CH=CH	23,000	nt

Table IV



Compound Number	R_2	HMG-CoA Reductase IC_{50} (nM)	Cell Culture Cholesterol Biosynthesis IC_{50} (μM)
47	Ph-CH_2	120	0.29
58	(3-MeO-Ph)-CH_2	210	0.80
60	(4-Cl-Ph)-CH_2	nt	0.46
62	(4-Me-Ph)-CH_2	70	0.20
64	(4-t-Bu-Ph)-CH_2	30	nt

Table V



Compound Number	R_2	HMG-CoA Reductase IC_{50} (nM)	Cell Culture Cholesterol Biosynthesis IC_{50} (μM)
79	Ph-CH_2	750	0.26
80	(2-Et)Bu	29,000	nt
81	(2-Nap)-CH_2	nt	0.39
82	(4-t-Bu-Ph)-CH_2	70	0.23
83	H	9,000	nt

The pharmaceutical compositions containing compounds of the present invention are comprised of the compounds of the present invention and a pharmaceutically acceptable carrier in either solid or liquid form. Solid form preparations include powders, tablets, dispersible granules, capsules, etc. The carrier may also be one or more substances which act as diluents, flavoring agents, solublizers, lubricants, suspending agents, binders, or tablet disintegrating agents and they may also be encapsulating materials. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, peptin, dextrin, starch, methyl cellulose, sodium carboxyl methyl cellulose, and the like. Liquid form preparations include solutions which are suitable for oral or parenteral administration, or suspensions and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active components in solvents comprising water, ethanol, or propylene glycol are examples of liquid preparations suitable for parenteral administration. Sterile

solutions may be prepared by dissolving the active component in the desired solvent system, then passing the resulting solution through a membrane filter to sterilize it, or alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions. Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers and thickening agents as required. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as a natural or synthetic gum, resin methyl cellulose, sodium carboxy methyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage form" as used in the specification and claims herein refers to physically discrete units suitable as unit dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

In therapeutic use as hypolipidemic or hypocholesterolemic agents, the compounds utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from about 0.01-100 mg/kg per day. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of optimum dosages for a particular situation is within the skill of the art.

In the following examples, Examples 13, 14, 20 and 21, Tables 8, 9A, 9B, 13A, 13B, and 14, illustrate the preparation of the final compounds **I(a-c)** according to the present invention. Examples 3 and 11, Tables 3A, 3B, and 6, illustrate the preparation of the novel intermediate of the compound of formula **X**. The remainder of the examples illustrate the preparations of the various intermediates according to the reaction scheme set forth previously that are made to produce the compounds of the present invention. For ease of reference, each example is keyed to a particular step in the reaction scheme. Moreover, there are specific examples of one compound for each step in the sequence and a general procedure for making the other compounds which are listed in the table at the end of each example.

Unless otherwise noted, materials used in the examples were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from Na/benzophenone immediately prior to use. The following chemicals were obtained from Sigma Chemical Co: digitonin, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), and β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH). The (1-^{14}C)-acetate was obtained from both Research Biochemicals, Inc. (RBI) and New England Nuclear-Dupont (NEN). The (3-^{14}C)-HMG-CoA was obtained from NEN, and (7-^{3}H)-cholesterol and (7-^{3}H)-cholesteryl oleate were obtained from Amersham. HI-FBS (heat-inactivated fetal bovine serum) and calf serum were obtained from Grand Island Biological Co. (GIBCO). Lovastatin was obtained from Merck. Lovastatin-Na was prepared from Lovastatin by reaction with sodium hydroxide. Pravastatin was obtained from Sigma, and XU-62320 was obtained from Sandoz. Diisopropylamine was distilled from CaH_2 and was stored over 4A molecular sieves. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used without purification. Dimethylformamide (DMF) was dried over 4A sieves prior to use. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard using the following spectrometers: Bruker WP-100SY (100 MHz ^{1}H, 25 MHz ^{13}C), General Electric QE-300 (300 MHz ^{1}H, 75 MHz ^{13}C), Varian XL-400 (400 MHz ^{1}H, 100 MHz ^{13}C). NMR chemical shifts are expressed in parts per million (ppm) downfield from internal TMS using the δ scale. ^{1}H Hertz). ^{13}C NMR data are reported for proton-decoupled spectra and are tabulated in order. Infrared (IR) spectra were determined on a Nicolet 5DXB FT-IR spectrophotometer. Chemical ionization (DCI), electron impact (EI), and fast atom bombardment (FAB) mass spectra (MS) were determined on a Finnegan MAT 8230 spectrometer. Elemental analyses were carried out on a Perkin Elmer 240C analyzer. Analytical thin layer chromatography (TLC) was done with Merck Silica Gel 60 F_{254} plates (250 micron). Flash chromatography and medium pressure liquid chromatography (MPLC) were done with Merck Silica Gel 60 (230-400 mesh).

EXAMPLE 1

2-[(1,1'-Biphenyl)-4-ylmethyl]cyclohexanone (Compound (hereinafter CP) 84, Reaction Scheme (hereinafter RS) Step a):

A 1.3 M solution of s-BuLi in hexanes (51.8 mmol, 39.8 mL) was added over a 15 min period to a -78 °C solution containing 9.29 g (51.8 mmol) of N-cyclohexylidine cyclohexylamine (Stork, G., Dowd, S. R. J. Am. Chem. Soc., 1963 85, 2178-80) in 75 mL of THF under N_2. After 30 min, the cooling bath was removed and the cloudy solution was allowed to warm to 0°C. A solution of 10.0 g (49.3 mmol) of 4-(chloromethyl)biphenyl

in 30 mL of THF was added and the resulting mixture was stirred at room temperature overnight. A 40 mL portion of 2 N aqueous HCl was added and the mixture was stirred for 5 h. Et_2O (200 mL) was added and the organic solution was washed successively with water, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated to give 13.1 g of an off-white solid. Recrystallization from EtOAc:hexanes afforded 9.22 g. (71%) of the title compound as a white solid, m.p. 78-79 °C; ^1H NMR ($CDCl_3$, 300 MHz) 1.40 (m, 1), 1.65 (m, 2), 1.83 (m, 1), 2.10 (m, 2), 2.35 (m, 1), 2.52 (m, 2), 2.60 (m, 1), 3.27 (dd, 1, J=5, 13.5 Hz), 7.2-7.6 (complex); IR (KBr) 1695 cm^{-1}; MS (DCI) m/z 265 (base). Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.66; H, 7.98.

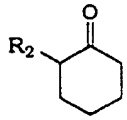
General procedure for the preparation of 2-substituted cyclohexanones shown in Table 1:

Method A (RS step a): *s*-BuLi (50 mmol) was added under N_2 to a solution of 50 mmol of the cyclohexylimine of N-cyclohexylidine cyclohexylamine in 75 mL of THF at -78 °C. The resulting cloudy solution was stirred for 30 min and was allowed to warm to 0°C. A solution of 48 mmol of the appropriate alkyl or aralkyl halide in a minimum volume of THF was added dropwise and the solution was allowed to warm to room temperature and was stirred overnight. A 50 mL portion of 2 N aqueous HCl (100 mmol) was added and the two phase mixture was stirred vigorously until TLC analysis showed that hydrolysis of the imine was complete (2-8 h). The mixture was extracted with Et_2O or EtOAc and the organic layer was washed with water, saturated aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4 and concentration, the crude product was purified by either MPLC or vacuum distillation using a short path still.

Alternatively, a solution of 50 mmol of the appropriate cyclohexylimine in a minimum volume of THF was added dropwise under N_2 to an ice-cold stirring solution of 52.5 mmol of lithium diisopropylamide (LDA, generated by the addition of 55 mmol of diisopropylamine in 35 mL of THF to 52.5 mmol of a 1.6 M hexanes solution of *n*-BuLi at 0°C). After 30-45 min, a solution of 48 mmol of the appropriate alkyl or aralkyl halide in a minimum volume of THF was added dropwise and the mixture was allowed to warm to room temperature and was stirred overnight. A 75 mL portion of 2 N aqueous HCl (150 mmol) was added and the two phase mixture was stirred vigorously until TLC analysis showed that hydrolysis of the imine was complete (4-24 h). The reaction mixture was worked up as described above.

Method B (RS step b): An ice-cold suspension of oil-free NaH (150 mmol) in 120 mL of a 1:1 mixture of benzene and DMF was treated, dropwise, with ethyl 2-cyclohexanonecarboxylate (145 mmol) in 60 mL of the same solvent mixture over a 30 min period. The mixture was stirred an additional 30 min and 140 mmol of the appropriate alkyl or aralkyl halide in a minimum amount of benzene was added dropwise. After stirring at room temperature for 2-3 days, 250 mL of Et_2O was added and the organic solution was washed with water (3 x 100 mL) and brine. Drying (Na_2SO_4) and concentration gave the crude alkylated keto ester which was dissolved in 100 mL each of HOAc and 6 N aqueous HCl and refluxed until TLC analysis showed that the hydrolysis/decarboxylation was complete (2-3 days). Most of the solvent was removed by rotary evaporation and the residue was partitioned between water (100 mL) and Et_2O (300 mL). The Et_2O layer was washed with brine, dried over Na_2SO_4, and concentrated to give the crude product which was purified as described in Method A above.

Table 1



Compound Number	Method	R_2	bp (°C)	Mass spectrum m/z $[M+H]^+$
85	A	(1-Nap)-CH_2	oil	239
86	B	(2-Cl-Ph)-CH_2	129-135 (0.4 Torr)	223
87	A	(2-Nap)-CH_2	180-190 (0.6 Torr)	239
88	A	(3-MeO-Ph)-CH_2	190-195 (4 Torr)	219
89	A	(3,4-di-MeO-Ph)-CH_2	180-187 (1 Torr)	249
90	A	(4-Cl-Ph)-CH_2	150-170 (0.1 Torr)	223
91	B	(4-F-Ph)-CH_2	110-125 (0.5 Torr)	207
92	A	(4-i-Pr-Ph)-CH_2	90-160 (0.1 Torr)	231
93	A	(4-Me-Ph)-CH_2	oil	203
94	B	(4-MeO-Ph)-CH_2	155-170 (0.6 Torr)	219
95	A	(4-t-Bu-Ph)-CH_2	136-148 (0.5 Torr)	245
96	A	Ph-$(CH_2)_2$	124-130 (0.5 Torr)	203
97	A	Ph-$(CH_2)_3$	100-200 (0.8 Torr)	217
98	A	Ph-CH=CH-CH_2	160-170 (0.8 Torr)	215

EXAMPLE 2

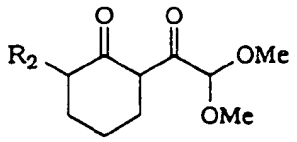
6-[(1,1'-Biphenyl-4-yl)methyl]-2-(2,2-dimethoxy-1-oxoethyl)cyclohexanone (CP 99, RS step c):

Diisopropylamine (38.8 mmol, 3.93 g, 5.4 mL) was added under N_2 to a -20°C solution of 1.6 M *n*-BuLi in hexanes (35.3 mmol, 22.0 mL) and 30 mL of THF. After 15 min, the solution was cooled to -78°C and 8.88 g (33.6 mmol) of Compound 84 in 50 mL of THF was added. After 45 min, 2.26 mL (18.5 mmol, 2.48 g) of methyl dimethoxyacetate was added and the mixture was allowed to warm slowly to room temperature and was stirred overnight. The resulting solution was cooled to 0°C and acidified to pH 3-4 with 2N aqueous HCl. The mixture was diluted with Et_2O (200 mL) and washed with water and brine. After drying over Na_2SO_4, the solution was concentrated to give 11.5 g of a yellow oil. The crude product was purified by MPLC using a solvent gradient ranging from 1:6 to 1:5 EtOAc:hexanes to afford 5.94 g (96%) of the title compound as a waxy, white solid; ^1H NMR ($CDCl_3$, 300 MHz) 1.4-2.8 (complex, 9), 3.33 (s, 3, minor tautomer), 3.37 (s, 3, minor tautomer), 3.42 (s, 6, major tautomer), 4.63 (s, 1, minor tautomer), 4.96 (s, 1, major tautomer), 7.2-7.6 (complex, 9) ; IR (KBr) 1739, 1704, 1601, 1584, 1488, 1444 cm^{-1}; MS (DCI) m/z 335 (base), 303. Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.64; H, 7.39.

General procedure for the preparation of 6-substituted diketones shown in Table 2 (RS step c):

Diisopropylamine (57.8 mmol) was added under N_2 to a -20°C solution of 52.5 mmol of a 1.6 M hexanes solution of *n*-BuLi and 45 mL of THF. (Alternatively, 52.5 mmol of a 1.0 M solution of $LiN(SiMe_3)_2$ in THF/cyclohexane was added to 25 mL of THF under N_2 at -20°C.) After 15 min, the solution was cooled to -78 °C and 50.0 mmol of the appropriately substituted cyclohexanone (from Table 1, or commercially available) in 50 mL of THF was added. After 45 min, 27.5 mmol of methyl dimethoxyacetate was added and the mixture was allowed to warm slowly to room temperature. After stirring overnight, the resulting solution was cooled to 0°C and acidified to pH 3-4 with 2N aqueous HCl. The mixture was diluted with Et_2O (200 mL) and washed with water and brine. After drying over Na_2SO_4, the solution was concentrated to give the crude product, which was purified by MPLC.

Table 2



Compound Number	R_2	mp (°C)	Mass spectrum m/z [MH-MeOH]$^+$
100	(1-Nap)-CH_2	oil	309
101	(2-Cl-Ph)-CH_2	oil	293
102	(2-Et)Bu	oil	225
103	(2-Nap)-CH_2	oil	309
104	(3-MeO-Ph)-CH_2	oil	289
105	(3,4-di-MeO-Ph)-CH_2	oil	319
106	(4-Cl-Ph)-CH_2	oil	293
107	(4-F-Ph)-CH_2	oil	277
108	(4-i-Pr-Ph)-CH_2	oil	301
109	(4-Me-Ph)-CH_2	oil	273
110	(4-MeO-Ph)-CH_2	oil	289
111	(4-t-Bu-Ph)-CH_2	oil	315
112	c-Hex	oil	251
113	Et	oil	197
114	Me	oil	183
115	n-Pr	oil	211
116	Ph	oil	245
117	Ph-CH_2	oil	259
118	Ph-$(CH_2)_2$	oil	273
119	Ph-$(CH_2)_3$	oil	287
120	Ph-CH=CH-CH_2	oil	285
121	s-Bu	oil	225

EXAMPLE 3

7-[(1,1'-Biphenyl-4-yl)methyl]-2-(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxaldehyde (CP 122, RS step g) and 7-[(1,1'-Biphenyl-4-yl)methyl]-1-(4-fluorophenyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxaldehyde (CP 123 RS step g):

A solution of Compound 99 (20.2 mmol, 5.35 g) in 100 mL of absolute EtOH was treated with 1.91 g (23.3 mmol) of NaOAc and 3.45 g (21.2 mmol) of 4-fluorophenylhydrazine · HCl. After stirring overnight under N_2, the solvent was removed by rotary evaporation and the orange residue was dissolved in 100 mL of THF. A 50 mL portion of 1N aqueous HCl was added and the mixture was stirred and refluxed gently for 4 h. Et_2O (150 mL) was added after cooling and the organic layer was washed sequentially with water, saturated aqueous $NaHCO_3$, and brine. Drying over Na_2SO_4 and concentration afforded 6.74 g of an orange foam. The crude product was purified by MPLC using 1:9 EtOAc:hexanes to give 1.90 g (23%) of the 2-(4-fluorophenyl) isomer and 1.15 g (14%) of the 1-(4-fluorophenyl) isomer, each as an orange solid. The 2-(4-fluorophenyl) isomer was recrystallized from EtOAc:Et_2O to afford Compound 122 as a pale orange solid, m.p. 148-150°C; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.6-2.0 (complex, 4), 2.72 (dd, 1, J=10.5, 13.5 Hz), 2.75-3.0 (complex), 3.15 (m, 1), 3.56 (dd, 1, J=4, 13.5 Hz), 7.2-7.7 (complex, 13), 9. 87 (s, 1); IR (KBr) 1510, 1222 cm^{-1}; MS (DCI) m/z 411 (base). HRMS (EI) Cacld for $C_{27}H_{23}FN_2O$: 410.179428. Found: 410.175457.

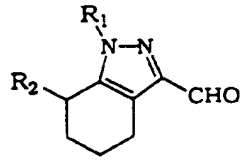
The 1-(4-fluorophenyl) isomer was recrystallized from EtOAc:hexanes to provide analytically pure Compound 123 as an orange solid, m.p. 155-156; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.7-1.9 (complex, 4), 2.46 (dd, 1, J=10.5, 13.5 Hz), 2.61 (dd, 1, J=4, 13.5 Hz), 2.73 (dt, 1, J=16.5, 8 Hz), 3.02 (dt, 1, J=16.5, 4 Hz), 3.30 (m, 1), 6.89 (d, 2, J=8 Hz), 7.2-7.6 (complex, 11), 10.08 (s, 1); IR (KBr) 1691, 1512 cm^{-1}; MS (DCI) m/z 411 (base).

Anal. Calcd. for $C_{27}H_{23}FN_2O$: C, 79.00; H, 5.65; N, 6.82. Found: C, 79.22; H, 5.54; N, 6.61.

General procedure for the preparation of 7-substituted 4,5,6,7-tetrahydroindazole-3-carboxaldehydes shown in Tables 3A and 3B (RS step g):

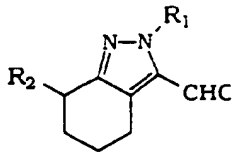
A solution of 10 mmol of the appropriately substituted diketone from Table 2 in 100 mL of absolute EtOH or MeOH was treated with 11.5 mmol of a base (NaOAc, Et_3N, or pyridine) and 10.5 mmol of the appropriately substituted hydrazine hydrochloride. After stirring overnight under N_2, the solvent was removed by rotary evaporation and the residue was dissolved in 50 mL of THF. A 25 mL portion of IN aqueous HCl was added and the mixture was stirred and refluxed gently for 4 h. After cooling, 100 mL of Et_2O was added and the organic layer was washed sequentially with water, saturated aqueous $NaHCO_3$, and brine. Drying over Na_2SO_4 and concentration afforded the crude product as a mixture of 2-aryl and 1-aryl isomers in ratios ranging from 1:1 to 1:3. The crude mixture was purified by recrystallization and/or MPLC; the 2-aryl isomer eluted before the 1-aryl isomer in all cases.

Table 3A



Compound Number	R_1	R_2	mp (°C)	Mass Spectrum [M+H]+
124	4-F-Ph	(1-Nap)-CH_2	183-184	385
125	4-F-Ph	(2-Cl-Ph)-CH_2	137-138	369
126	4-F-Ph	(2-Et)Bu	121-122	329
127	4-F-Ph	(2-Nap)-CH_2	foam	385
128	4-F-Ph	(3-MeO-Ph)-CH_2	93-94	365
129	4-F-Ph	(3,4-di-MeO-Ph)-CH_2	117-119	395
130	4-F-Ph	(4-Cl-Ph)-CH_2	134-135	369
131	4-F-Ph	(4-F-Ph)-CH_2	128-131	353
132	4-F-Ph	(4-i-Pr-Ph)-CH_2	112-113	377
133	4-F-Ph	(4-Me-Ph)-CH_2	117-118	349
134	4-F-Ph	(4-MeO-Ph)-CH_2	104-107	365
135	4-F-Ph	(4-t-Bu-Ph)-CH_2	139-140	391
136	4-F-Ph	c-Hex	119-121	327
137	4-F-Ph	Et	95-97	273
138	4-F-Ph	Me	124-125	259
139	4-F-Ph	n-Pr	oil	287
140	4-F-Ph	Ph	71-73	321
141	4-F-Ph	Ph-CH_2	144-145	335
142	4-F-Ph	Ph-$(CH_2)_2$	97-99	349
143	4-F-Ph	Ph-$(CH_2)_3$	oil	363
144	4-F-Ph	Ph-CH=CH-CH_2	106-108	361
145	4-F-Ph	s-Bu	86-89	301
296	*t*-Bu	(1-Nap)-CH_2	119-120	347

Table 3B



Compound Number	R_1	R_2	mp (°C)	Mass Spectrum [M+H]+
146	4-F-Ph	(1-Nap)-CH_2	116-117	385
147	4-F-Ph	(2-Cl-Ph)-CH_2	glass	369
297	4-F-Ph	(2-Et)Bu	foam	329
148	4-F-Ph	(2-Nap)-CH_2	122-123	385
149	4-F-Ph	(3-MeO-Ph)-CH_2	foam	365
150	4-F-Ph	(3,4-di-MeO-Ph)-CH_2	109-110	395
151	4-F-Ph	(4-Cl-Ph)-CH_2	126-128	369
152	4-F-Ph	(4-F-Ph)-CH_2	oil	353
153	4-F-Ph	(4-i-Pr-Ph)-CH_2	oil	377
154	4-F-Ph	(4-Me-Ph)-CH_2	foam	349
155	4-F-Ph	(4-MeO-Ph)-CH_2	oil	365
156	4-F-Ph	(4-t-Bu-Ph)-CH_2	124-125	391
157	4-F-Ph	c-Hex	oil	327
158	4-F-Ph	Et	72-74	273
159	4-F-Ph	Me	79-80	259
160	4-F-Ph	n-Pr	50-53	287
161	4-F-Ph	Ph	139-140	321
162	4-F-Ph	Ph-CH_2	99-100	335
163	4-F-Ph	Ph-$(CH_2)_2$	89-90	349
164	4-F-Ph	Ph-$(CH_2)_3$	100-102	363
165	4-F-Ph	Ph-CH=CH-CH_2	104-105	361
166	4-F-Ph	s-Bu	oil	301
298	*t*-Bu	(1-Nap)-CH_2	142-143	347

EXAMPLE 4

3-Acetoxymethyl-2-(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-indazole (CP 167, RS step h):

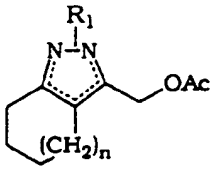
Et_3N (0.717 mL, 0.520 g, 5.14 mmol) was added to a stirring suspension of 1.00 g (5.04 mmol) of 2-acetoxyacetylcyclohexanone (Dolmazon, R.; Gelin, S. J. Heterocyclic Chem., 1982, 19, 117-121) and 0.820 g (5.04 mmol) of 4-fluorophenylhydrazine · HCl in 20 mL of absolute EtOH. The resulting solution was stirred under N_2 for 4 h at room temperature and refluxed for 6 h. The mixture was concentrated and the residue was partitioned between 100 mL of Et_2O and 50 mL of dilute aqueous HCl. The Et_2O layer was washed with water, saturated aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4, the solution was concentrated to give 1.43 g of light brown solid. Recrystallization from EtOAc:hexanes afforded 0.753 g (52%) of the title compound as a white solid, m.p. 128.5-129.5 °C; ^1H NMR ($CDCl_3$, 400 MHz) 1.85 (m, 4), 2.07 (s, 3), 2.60 (t, 2, J=6 Hz), 2.73 (t, 2, J=6 Hz), 5.00 (s, 2), 7.15 (t, 2, J=9 Hz), 7.45 (dd, 2, J=5, 9 Hz); IR (KBr) 1740, 1220 cm^{-1}; MS (DCI) m/z 289 (base), 228. Anal. Calcd. for $C_{16}H_{17}FN_2O_2$: C, 66.65; H, 5.94; N, 9.72. Found: C, 66.74; H, 5.89; N, 9.61.

General procedure for the preparation of acetates shown in Table 4 (RS step h):

A mixture of 10 mmol of the appropriate 2-acetoxyacetylcycloalkanone (2-acetoxyacetylcyclopentanone, Dolmazon, R. J. Heterocyclic Chem., 1988, 25, 751-7; 2-acetoxyacetylcyclohexanone, Dolmazon, R.; Gelin, S. J. Heterocyclic Chem., 1982 19, 117-21), 10.5 mmol of Et_3N, and 10 mmol of appropriately substituted hydrazine in 40 mL of absolute EtOH was stirred under N_2 for 4-5 h and refluxed for 6-8 h. The solvent was evaporated and the resulting residue was partitioned between Et_2O and 0.1 N HCl. The Et_2O layer was washed with

water, saturated aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4, the solution was concentrated and the crude product was purified by recrystallization and/or MPLC. The 2-acetoxyacetylcyclopentanone reaction afforded a 9:1 mixture of 1-aryl:2-aryl isomers, while the 2-acetoxyacetylcyclohexanone reaction gave only the 2-aryl isomer.

Table 4



Compound Number	n	R_1	mp (°C)	Mass Spectrum [M+H]+
168	0	1-(4-F-Ph)	85-86	275
169	0	2-(4-F-Ph)	87-88	275
170	1	2-(4-Cl-Ph)	oil	305

EXAMPLE 5

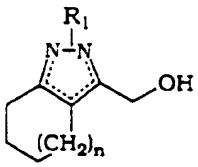
2-(4-Fluorophenyl)-4,5,6,7-tetrahydro-2H-indazole-3-methanol (CP 171, RS step i):

Compound 167 (24.3 mmol, 7.00 g) was dissolved in 125 mL of MeOH and stirred while 26.7 mL of 1N aqueous NaOH was added. After 30 min the resulting cloudy suspension was concentrated and partitioned between 200 mL of EtOAc and 100 mL of water. The organic layer was washed with water and brine and was dried over Na_2SO_4. The solution was concentrated to give 5.85 g of orange solid. Recrystallization from EtOAc gave 4.08 g (68%) of the title compound as off-white crystals, m.p. 163-164 °C; ^1H NMR ($CDCl_3$, 400 MHz) 1.80 (m, 4), 2.52 (t, 1, J=5 Hz), 2.86 (t, 2, J=6 Hz), 2.71 (t, 2, J=6 Hz), 4.52 (d, 2, J=5 Hz), 7.12 (2, t, J=9 Hz), 7.58 (dd, 2, J=5, 9 Hz); ^{13}C NMR (DMSO-d_6, 25 MHz) 19.8, 23.0 (triple), 52.1, 115.7 (d, J_{C-F} = 23 Hz), 116.6, 125.2 (d, J_{C-F} = 8 Hz), 136.5, 137.9, 148.8, 160.6 (d, J_{C-F} = 244 Hz); IR (KBr) 3200 (broad), 1510 cm^{-1}; MS (DCI) m/z 247 (base). Anal. Calcd. for $C_{14}H_{15}FN_2O$: C, 68.28; H, 6.14; N, 11.37. Found: C, 68.47; H, 6.02; N, 11.35.

General procedure for the preparation of alcohols shown in Table 5 (RS step i):

The appropriate acetate from Table 4 (10 mmol) was dissolved in 50 mL of MeOH and stirred while 11 mmol of 1 N aqueous NaOH was added. The resulting suspension was stirred 0.5-24 h and worked up by one of two methods. In the first method, the mixture was concentrated and partitioned between water and solvent. The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. Alternatively, the reaction mixture was filtered to remove the solids and the filtrate was treated with water to precipitate the remaining product. The combined solids were dissolved in $CHCl_3$, washed with brine, and concentrated. The crude product was purified by recrystallization or a combination of recrystallization and MPLC.

Table 5



Compound Number	n	R_1	mp (°C)	Mass Spectrum [M+H]+
172	0	1-(4-F-Ph)	85-86	233
173	0	2-(4-F-Ph)	170-171	233
174	1	2-(4-Cl-Ph)	184.5-185	263

EXAMPLE 6

2-(4-Fluorophenyl)-2,4,5,6,7,8-hexahydrocycloheptapyrazole-3-methanol (CP 175, RS step e, followed by RS step k):

A solution of 2.80 g (25 mmol) of cycloheptanone and 4.71 g (25 mmol) of ethyl (tetrahydropyranyloxy) acetate (Ireland, R.E.; Wipf, P. Tetrahedron Lett., 1989, 30, 919-22) in 20 mL of Et_2O was added over the course of 1 h to an ice-cold, stirring mixture of hexane-washed NaH and 0. 12 mL (2 mmol, 0.092 g) of absolute EtOH in 10 mL of Et_2O under N_2. The light brown mixture was allowed to warm to room temperature and was stirred overnight. MeOH (5 mL) was added and the solution was poured onto 200 mL of saturated aqueous NH_4Cl. After acidification to pH 2 with 1 N aqueous HCl, the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give 5.61 g of crude 2-[(tetrahydropyranyloxy)acetyl]cycloheptanone as a light brown oil.

The crude diketone was dissolved in 60 mL of absolute EtOH and combined with 3.07 mL (22 mmol, 2.23 g) of Et_3N and 3.45 g (21.1 mmol) of 4-fluorophenylhydrazine · HCl. The resulting solution was stirred under N_2 overnight and refluxed for 4 h. A 30 mL portion of 1 N aqueous HCl was added and the mixture was refluxed for an additional hour. The mixture was cooled and extracted with 200 mL of Et_2O. The organic phase was washed with water, saturated aqueous $NaHCO_3$, and brine and dried over Na_2SO_4. The solution was concentrated to give 5.50 g of a 1.2:1 mixture of 1-(4-fluorophenyl)-1,4,5,6,7,8-hexahydrocycloheptapyrazole-3-methanol and the title compound as a brown oil. The crude product was crystallized from EtOAc:Et_2O to afford 0.97 g (18%) of the title compound as an off-white solid, m.p. 177-178 °C; ^1H NMR ($CDCl_3$, 300 MHz) 1.72 (m, 4), 1.85 (m, 2), 2.60 (m, 2), 2.80 (m, 2), 4.51 (d, 2, J=5 Hz), 7.15 (m, 2), 7.60 (m, 2); IR (KBr) 3240 (broad), 1513, 1223 cm^{-1}; MS (DCI) m/z 261 (base). Anal. Calcd. for $C_{15}H_{17}FN_2O$: C, 69.21; H, 6.58; N, 10.76. Found: C, 69.15; H, 6.77; N, 10.63.

EXAMPLE 7

Ethyl 2,4,5,6,7,8-hexahydrocycloheptapyrazole-3-carboxylate (CP 176, RS step f, followed by RS step 1):

Hydrazine hydrate (30.3 mmol, 1.52 g, 1.47 mL) was added dropwise under N_2 to a stirring solution of ethyl α,2-dioxocycloheptaneacetate (Tsuboi, S.; Nishiyama, E.; Furutani, H.; Utaka, M.; Takeda, A. J. Org. Chem., 1987, 52, 1359-62) in 60 mL of MeOH. The reaction mixture, which had become warm during the addition, was allowed to cool to room temperature and was stirred overnight. The solvent was evaporated and the resulting oil was dissolved in CH_2Cl_2 and washed with water and brine. After drying over Na_2SO_4, the solution was concentrated to give 6.36 g of pale yellow solid. Recrystallization from EtOAc:hexanes afforded 3.44 g (52%) of the title compound as a white solid, m.p. 90-92 °C; ^1H NMR ($CDCl_3$, 300 MHz) 1.38 (t, 3, J=7 Hz), 1.67 (m, 4), 1.84 (m, 2), 2.80 (m, 2), 2.93 (m, 2), 4.37 (q, 2, J=7 Hz), 7.0 (broad s, 1); IR (KBr) 1719 cm^{-1}; MS (DCI) m/z 209 (base). Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.48; H, 7.76; N, 13.64.

EXAMPLE 8

Ethyl 2-(4-fluorobenzyl)-2,4,5,6,7,8-hexahydrocycloheptapyrazole-3-carboxylate (CP 177, RS step m) and ethyl 1-(4-fluorobenzyl)-1,4,5,6,7,8-hexahydrocycloheptapyrazole-3-carboxylate (CP 178, RS step m):

A solution of 7.90 g (37.9 mmol) of Compound 176 in 35 mL of DMF was added dropwise under N_2 to a suspension of hexane-washed NaH (41.7 mol, 1.67 g of a 60% oil suspension) in 20 mL of DMF. When the addition was complete, the mixture was heated at 140°C with an oil bath for 15 min. A solution of 5.00 mL (41.7 mmol, 6.03 g) of 4-fluorobenzyl chloride in 5 mL of DMF was added and the mixture was heated for an additional 30 min. After cooling, 400 mL of Et_2O was added and the solution was poured onto 250 mL of saturated aqueous NH_4Cl. The aqueous layer was extracted with two 50 mL portions of Et_2O and the combined organic phases were washed with three 100 mL portions of water and once with brine. The organic solution was dried over Na_2SO_4 and concentrated to give 11.9 g of a 1:1 mixture of the title compounds as a yellow oil. Purification by MPLC afforded, in the earlier fractions, 3.85 g (32%) of pure 2-(4-fluorobenzyl) isomer as a colorless oil; ^1H NMR ($CDCl_3$, 100 MHz) 1.31 (t, 3, J=7 Hz), 1.70 (m, 6), 2.83 (m, 4), 4.29 (q, 2, J=7 Hz), 5.58 (s, 2), 6.9-7.4 (complex, 4). The later-eluting fractions contained 4.94 g (42%) of the 1-(4-fluorobenzyl) isomer as a colorless oil; ^1H NMR ($CDCl_3$, 100 MHz) 1.40 (t, 3, J=7 Hz), 1.4-2.0 (complex, 6), 2.55 (m, 2), 2.95 (m, 2), 4.41 (q, 2, J=7 Hz), 5.35 (s, 2), 7.00 (m, 4).

EXAMPLE 9

2-(4-Fluorobenzyl)-2,4,5,6,7,8-hexahydrocycloheptapyrazole-3-methanol (CP 179, RS step n):

A solution of 1.43 g (4.52 mmol) of Compound 177 in 13 mL of THF under N_2 was added dropwise over a 10 min period to an ice cold suspension of 0.113 g (2.83 mmol) of $LiAlH_4$ in 7 mL of THF. After 30 min in the cold, the suspension was allowed to warm to room temperature and was stirred for 2 h. Et_2O (50 mL) was added, followed sequentially by 0.12 mL of water, 0.12 mL of 15% aqueous NaOH, and 0.36 mL of water, dropwise over a 1 h period. The white suspension was stirred overnight, treated with $MgSO_4$, and stirred 30 min more. The solids were removed by filtration and were washed with CH_2Cl_2. The combined filtrates were concentrated to afford 1.24 g of a white solid, which was recrystallized to give 0.998 g (80%) of the title compound as white needles, m.p. 156-157 °C; ^1H NMR ($CDCl_3$, 300 MHz) 1.55-1.70 (complex, 7), 1.82 (m, 2), 2.47 (m, 2), 2.74 (m, 2), 4.48 (d, 2, J=6 Hz), 5.27 (s, 2), 6.98 (t, 2, J=7 Hz), 7.12 (m, 2); IR (KBr) 3170 (broad), 1517, 1231, 1016 cm^{-1}; MS (DCI) m/z 275 (base), 257. Anal. Calcd. for $C_{16}H_{19}FN_2O$: C, 70.05; H, 6.98; N, 10.21. Found: C, 69.98; H, 6.98; N, 10.28.

EXAMPLE 10

1-(4-Fluorobenzyl)-1,4,5,6,7,8-hexahydrocycloheptapyrazole-3-methanol (CP 180, RS step n):

Following the procedure described above, 4.82 mmol (15.23 g) of Compound 178 gave 4.12 g (98%) of the title compound as an amber oil, which was used without purification; ^1H NMR ($CDCl_3$, 100 MHz) 1.70 (m, 6), 2.57 (m, 4), 3.0 (broad s, 1), 4.59 (d, 2, J=6 Hz), 5.20 (s, 2), 7.00 (m, 4).

EXAMPLE 11

2-(4-Fluorophenyl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxaldehyde (CP 181, RS step j):

Pyridinium chlorochromate (22.0 mmol, 4.74 g) was suspended in 50 ml of CH_2Cl_2. Compound 171 (14.8 mmol, 3.64 g) was added in small portions over a 5 min period and the resulting suspension was stirred at room temperature for 4 h. A 300 mL portion of Et_2O was added and the mixture was filtered through a pad of Florisil. The tarry residue remaining in the flask was sonicated twice with 100 mL of Et_2O and the organic solutions were also filtered through Florisil. The Florisil pad was washed thoroughly with Et_2O and the combined organic solutions were dried over Na_2SO_4 and concentrated to give 3.57 g of an off-white solid. The crude product was recrystallized from Et_2O:hexanes to give 1.71 g (42%) of white crystals, m.p. 80-81 °C (the mother liquors were concentrated to give 1.67 g (47%) of a white solid which was judged to be pure enough to carry on); ^1H NMR ($CDCl_3$, 400 MHz) 1.85 (m, 4), 2.77 (t, 2, J=6 Hz), 2.88 (t, 2, J=6 Hz), 7.20 (m, 2), 7.45 (m, 2), 9.86 (s, 1); IR (KBr) 1670, 1575 cm^{-1}; MS (DCI) m/z 245 (base). Anal. Calcd. for $C_{14}H_{13}FN_2O$: C, 68.84; H, 5.36;

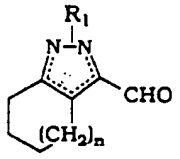
N, 11.47. Found: C, 68.79; H, 5.40; N, 11.39.

General procedure for the preparation of aldehydes shown in Table 6 (RS step j):

Method A: MnO_2 (100-120 mmol) was added in one portion to a stirring suspension of 10 mmol of the alcohol from Example 10 in 60 mL of benzene. The mixture was refluxed gently under N_2 until TLC analysis indicated that the starting material was completely consumed. After cooling, the slurry was filtered through a Celite pad and the black solids were washed with 250 mL of CH_2Cl_2. The filtrate was concentrated and the crude product was purified by MPLC or recrystallization.

Method B: To a stirring suspension of pyridinium chlorochromate (10 mmol) in 25 mL of CH_2Cl_2 was added, in approximately five portions, the appropriately substituted alcohol from Table 5 or Examples 5, 6, or 9, as a solid. The resulting suspension was stirred for 2-4 h at room temperature. Et_2O (150 mL) was added and the mixture was sonicated for 5-10 min. The supernatant was decanted through a pad of Florisil and the remaining solids were sonicated twice with 50 mL portions of Et_2O, which in turn were filtered. The Florisil pad was washed thoroughly with Et_2O and the combined filtrates were concentrated to give the crude product, which was purified by recrystallization.

Table 6



Compound Number	Method	n	R_1	mp (°C)	Mass spectrum m/z $[M+H]^+$
182	B	0	1-(4-F-Ph)	122-123	231
183	B	0	2-(4-F-Ph)	79-80	231
184	B	1	2-(4-Cl-Ph)	93-94	261
185	B	2	2-(4-F-Ph)	oil	259
186	A	2	1-(4-F-Ph-CH_2)	oil	273
187	B	2	2-(4-F-Ph-CH_2)	oil	273

EXAMPLE 12

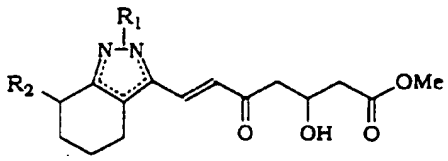
Methyl (E)-7-[7-[(1,1'-Biphenyl-4-yl)methyl]-2-(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]-3-hydroxy-5-oxo-6-heptenoate (CP 188, RS step t):

Compound 122 (2.68 mmol, 1.10 g), LiCl (3.08 mmol, 0.131 g), and 1.18 g (3.08 mmol) of methyl 3-[(*t*-butyldimethylsilyl)oxy]-6-(dimethoxyphosphinyl)-5-oxohexanoate (Theisen, P. D.; Heathcock, C. H. J. Org. Chem, 1988, 53, 2374-81) were combined in 15 mL of CH_3CN. DBU (2.95 mmol, 0.449 g, 0.441 mL) was added and the resulting clear, orange solution was stirred under N_2 for 6 h. The mixture was diluted with 100 mL of Et_2O and washed successively with 50 mL of 5% aqueous $NaHSO_4$, water, and brine. After drying over Na_2SO_4, the solution was concentrated to give 2.00 g of orange oil. The crude mixture was dissolved in 25 mL of CH_3CN, treated with 2.5 mL of 48% aqueous HF, and stirred for 5 h. Et_2O (100 mL) was added and the acid was quenched by careful addition of saturated aqueous $NaHCO_3$. The ethereal solution was washed with brine, dried over Na_2SO_4, and concentrated to give 1.54 g of orange foam. The crude product was purified by MPLC using 1:2 EtOAc:hexanes to afford 0.22 g (15%) of the title compound as a yellow solid and an additional 0.50 g (34%) as a pale yellow solid which crystallized directly from the chromatography fractions, m.p. 137-138 °C; ^1H NMR ($CDCl_3$, 300 MHz) 1.4-2.1 (complex, 4), 2.56 (d, 2, J=6 Hz), 2.71 (m, 3), 2.80 (d, 2, J=6 Hz), 3.15 (m, 1), 3.47 (d, 1, J =4 Hz), 3.56 (dd, 1, J=4, 13.5 Hz), 3.71 (s, 3), 4.52 (m, 1), 6.51 (d, 1, J=16 Hz), 7.1-7.7 (complex, 14); IR (KBr) 3450 (broad), 1734, 1603, 1512 cm^{-1}; MS (DCI) m/z 553, 451 (base). Anal. Calcd. for $C_{34}H_{33}FN_2O_4$: C, 73.89; H, 6.02; N, 5.07. Found: C, 73.94; H, 6.01; N, 5.03.

General procedure for the preparation of 7-substituted (E)-3-hydroxy-5-oxo-6-heptenoates shown in Table 7 (RS step t):

The appropriately substituted aldehyde (10 mmol) from Table 3A or 3B was combined with 11.5 mmol of LiCl and 11.5 mmol of methyl 3-[(*t*-butyldimethylsilyl)oxy]-6-(dimethoxyphosphinyl)-5-oxohexanoate in 25 mL of CH_3CN. DBU (11 mmol) was added and the resulting clear solution was stirred for 4-6 h, becoming slightly cloudy during that time. The mixture was diluted with 100 mL of Et_2O and washed successively with 100 mL of 5% aqueous $NaHSO_4$, water, and brine. After drying over Na_2SO_4, the solution was concentrated to give the crude silyloxy keto ester. The crude residue was dissolved in 100 mL of CH_3CN and was treated with 10 mL of 48% aqueous HF. After TLC analysis indicated complete consumption of silyloxy keto ester, 200 mL of Et_2O was added and the HF was quenched by careful addition of saturated aqueous $NaHCO_3$. The ethereal solution was washed with brine, dried over Na_2SO_4, and concentrated to give the crude product, which was purified by MPLC.

Table 7



Compound Number	R_1	R_2	mp (°C)	Mass Spectrum m/z $[M+H]^+$
189	1-(4-F-Ph)	Ph-$(CH_2)_2$	oil	491
190	2-(4-F-Ph)	(1-Nap)-CH_2	foam	527
191	2-(4-F-Ph)	(2-Nap)-CH_2	foam	527
192	2-(4-F-Ph)	(4-i-Pr-Ph)-CH_2	oil	519
193	2-(4-F-Ph)	(4-t-Bu-Ph)-CH_2	foam	533
194	2-(4-F-Ph)	Ph	foam	463
195	2-(4-F-Ph)	Ph-CH=CH-CH_2	oil	503

EXAMPLE 13

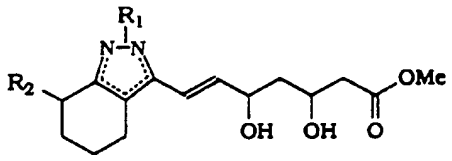
Methyl (E)-(3RS,5SR)-7-[7-[(1,1'-Biphenyl-4-yl)methyl]-2-(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]-3,5-dihydroxy-6-heptenoate (CP 39, RS step u):

Compound 188 (1.21 mmol, 0.67 g) was dissolved in 1.5 mL of MeOH and 5 mL of THF and treated, dropwise, with 1.33 mL (1.33 mmol) of a 1.0 M solution of Et_3B in THF. Air (5 mL) was bubbled into the solution *via* syringe and the resulting solution was stirred under N_2 for 2 h and then cooled to -78 °C. After addition of solid $NaBH_4$ in one portion, the mixture was allowed to warm slowly to room temperature and was stirred overnight. Et_2O (100 mL) and saturated aqueous NH_4Cl (50 mL) were added. The ethereal solution was washed with brine, dried over Na_2SO_4, and concentrated to give a yellow oil. The oil was dissolved in MeOH, stirred under air overnight, and concentrated to provide 0.74 g of pale yellow foam. Purification by MPLC using 45:55 EtOAc:hexanes afforded a white foam which crystallized upon addition of Et_2O, giving 281 mg (42%) of the title compound as a white solid, m.p. 118-119 °C (the mother liquors gave 77 mg (12%) of additional product as a white foam); ^1H NMR ($CDCl_3$, 300 MHz) 1.4-2.0 (complex, 6), 2.49 (d, 2, J=6 Hz), 2.6-2.8 (complex, 3), 3.10 (m, 1), 3.56 (dt, 1, J=13.5, 3.5 Hz), 3.62 (s, 1), 3.71 (s, 3), 3.78 (s, 1), 4.28 (m, 1), 4.48 (m, 1), 6.01 (dd, 1, J=6, 16 Hz), 6.45 (d, 1, J=16 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 21.6, 22.8, 27.9, 36.2, 40.3, 41.3, 42.7, 51.9, 68.3, 72.5, 115.7, 116.0 (J_{C-F} = 23 Hz), 118.0, 127.0, 127.3 (J_{C-F} = 8 Hz), 128.7, 129.8, 135.0, 135.3, 136.1, 138.8, 139.8, 141.1, 153.3, 161.7 (J_{C-F} = 247 Hz), 172.9; IR (KBr) 3400 (broad), 1734, 1513 cm^{-1}; MS (DCI) m/z 555 (base), 537, 523. Anal. Calcd. for $C_{34}H_{35}FN_2O_4$: C, 73.63; H, 6.36; N, 5.05. Found: C, 73.33; H, 6.60; N, 5.06.

General procedure for the preparation of 7-substituted (E)-(3RS,5SR)-3,5-dihydroxy-6-heptenoates shown in Table 8 (RS step u):

The appropriately substituted hydroxy keto ester from Table 7 (10 mmol), dissolved in 10 mL of MeOH and 30 mL of THF, was treated with 11 mmol of a 1.0 M THF solution of Et_3B. Air (about 20 mL) was bubbled into the solution *via* syringe and the resulting solution was stirred under N_2 for 2 h. After cooling to -78 °C, the solution was treated with 11 mmol of solid $NaBH_4$ in one portion, causing some gas evolution. The mixture was allowed to warm slowly to room temperature and was stirred overnight. Saturated aqueous NH_4Cl was added and the mixture was extracted with Et_2O. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to dryness. The residue, which smelled of excess Et_3B, was then dissolved in MeOH and stirred vigorously under air until TLC analysis showed complete conversion of the boron intermediates to the desired product (4-24 h). The MeOH was removed by rotary evaporation and the crude material was purified by MPLC.

Table 8



Compound Number	R^1	R_2	mp (°C)	Mass Spectrum m/z $[M+H]^+$
40	1-(4-F-Ph)	Ph-$(CH_2)_2$	foam	493
41	2-(4-F-Ph)	(1-Nap)-CH_2	foam	529
42	2-(4-F-Ph)	(2-Nap)-CH_2	foam	529
43	2-(4-F-Ph)	(4-i-Pr-Ph)-CH_2	foam	521
44	2-(4-F-Ph)	(4-t-Bu-Ph)-CH_2	foam	535
45	2-(4-F-Ph)	Ph	foam	465
46	2-(4-F-Ph)	Ph-CH=CH-CH_2	oil	505

EXAMPLE 14

(E)-(3RS,5SR)-7-[7-[(1,1'-Biphenyl-4-yl)methyl]-2-(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]-3,5-dihydroxy-6-heptenoic acid · Sodium salt · Dihydrate (CP 1, RS step v):

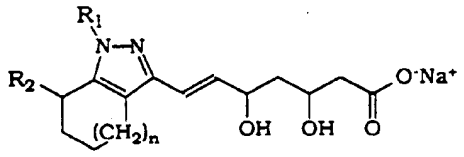
Aqueous NaOH (0.25 N, 0.392 mmol, 1.57 mL) was added slowly to an ice-cold solution of Compound 39 (0.400 mmol, 222 mg) in 10 mL of MeOH. When the addition was complete, the solution was allowed to warm to room temperature and stirred for 2 h. The solution was concentrated to dryness using a rotary evaporator and the residue was dissolved in 40 mL of water. The slightly cloudy solution was suction faltered through a coarse frit, frozen in a -78 °C bath, and lyophilized. The product was dried in a vacuum oven over Drierite to provide 219 mg (93%) of the title compound as a fluffy, white solid; ^1H NMR (DMSO-d_6, 400 MHz) 1.3-2.0 (complex, 7), 2.05 (dd, 1, J=4, 15 Hz), 2.4-2.7 (complex, 4), 3.01 (m, 1), 3.40 (m. 1), 3.75 (m, 1), 4.26 (m, 1), 5.13 (broad s, 1), 6.07 (dd, 1, J=5, 16 Hz), 6.36 (d, 1, J=16 Hz), 7.2-7.7 (complex, 13); IR (KBr) 3400 (broad), 1577, 1513 cm^{-1}; MS (FAB+) m/z 535, 563, 541, 167, 115 (base). Anal. Calcd. for $C_{33}H_{32}FN_2NaO_4 \cdot 2\ H_2O$: C, 66.21; H, 6.06; N, 4.68. Found: C, 66.39; H, 5.67; N, 4.62.

General procedure for the preparation of 7-substituted (E)-(3RS,5SR)-3,5-dihydroxy-6-heptenoic acid sodium salts shown in Tables 9A and 9B (RS step v):

Aqueous NaOH (0.25 N, 0.98 mmol) was added slowly to an ice-cold methanolic solution (15 mL) of 1.0 mmol of the appropriately substituted dihydroxy ester of Table 8, 13A, or 13B or Example 20. When the addition was complete, the solution was allowed to warm to room temperature and stir for 2 h until TLC analysis indicated that nearly all starting material had been consumed. The solution was concentrated to dryness using a

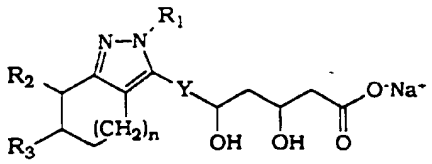
rotary evaporator and the residue was dissolved in 40 mL of water. The slightly cloudy solution was suction filtered through a coarse frit, frozen in a -78 °C bath, and lyophilized. The product was dried in a vacuum oven over Drierite to provide the desired sodium salt as a white, fluffy powder.

Table 9A



Compound Number	n	R_1	R_2	Mass Spectrum m/z $[M+H]^+$
2	0	4-F-Ph	H	383
3	1	4-F-Ph	(4-F-Ph)-CH_2	505
4	1	4-F-Ph	c-Hex	497
5	1	4-F-Ph	Et	425
6	1	4-F-Ph	Me	411
7	1	4-F-Ph	Ph-$(CH_2)_2$	501
8	1	4-F-Ph	Ph-CH=CH-CH_2	513
9	2	4-F-Ph-CH_2	H	425

Table 9B



Compound Number	n	R_1	R_2	R_3	Y	Mass Spectrum m/z $[M+H]^+$
10	0	4-F-Ph	H	H	CH=CH	383
11	1	4-F-Ph	(1-Nap)-CH_2	H	CH=CH	537
12	1	4-F-Ph	(2-Cl-Ph)-CH_2	H	CH=CH	521
13	1	4-F-Ph	(2-Nap)-CH_2	H	CH=CH	537
14	1	4-F-Ph	(3-MeO-Ph)-CH_2	H	CH=CH	517
15	1	4-F-Ph	(3,4-di-MeO-Ph)-CH_2	H	CH=CH	547
16	1	4-F-Ph	(4-Cl-Ph)-CH_2	H	CH=CH	520
17	1	4-F-Ph	(4-F-Ph)-CH_2	H	CH=CH	505
18	1	4-F-Ph	(4-i-Pr-Ph)-CH_2	H	CH=CH	529
19	1	4-F-Ph	(4-Me-Ph)-CH_2	H	CH=CH	501
20	1	4-F-Ph	(4-MeO-Ph)-CH_2	H	CH=CH	517
21	1	4-F-Ph	(4-t-Bu-Ph)-CH_2	H	CH=CH	543
22	1	4-F-Ph	------6,7-Benzo------		CH=CH	445
23	1	4-F-Ph	c-Hex	H	CH=CH	479
24	1	4-F-Ph	Et	H	CH=CH	425
25	1	4-F-Ph	H	H	CH=CH	397
26	1	4-Cl-Ph	H	H	CH=CH	413
27	1	4-F-Ph	H	H	CH=CMe	411
28	1	4-F-Ph	Me	H	CH=CH	411
29	1	4-F-Ph	n-Pr	H	CH=CH	439
30	1	4-F-Ph	Ph	H	CH=CH	473
31	1	4-F-Ph	Ph-CH_2	H	CH=CH	487
32	1	4-F-Ph	Ph-$(CH_2)_2$	H	CH=CH	501
33	1	4-F-Ph	Ph-$(CH_2)_3$	H	CH=CH	515
34	1	4-F-Ph	Ph-CH=CH-CH_2	H	CH=CH	513
35	1	4-F-Ph	s-Bu	H	CH=CH	453
36	2	4-F-Ph	------7,8-Benzo------		CH=CH	459
37	2	4-F-Ph	H	H	CH=CH	411
38	2	4-F-Ph-CH_2	H	H	CH=CH	425

EXAMPLE 15

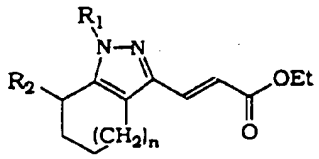
Ethyl (E)-3-[2-(4-fluorophenyl)-7-benzyl-4,5,6,7-tetrahydro-2H-indazol-3-yl]-2-propenoate (CP 196, RS step o):

Triethylphosphonoacetate (3.03 mmol, 0.706 g, 0.625 mL) in 2.5 mL of THF was added slowly under N_2 to a stirring suspension of oil-free NaH (3.09 mmol, 0.074 g) in 5 mL of THF. After 45 min, the solution was cooled in an ice bath and Compound 162 (2.75 mmol, 0.92 g) in 10 mL of THF was added dropwise. The mixture was allowed to warm to room temperature and was stirred overnight. Saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with 100 mL of Et_2O. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated to give 1.29 g of amber oil. The crude product was crystallized from Et_2O:hexanes to give 0.598 g (54%) of the title compound as an off-white solid, m.p. 117-118 °C; ^1H NMR ($CDCl_3$, 300 MHz) 1.30 (t, 3, J=7 Hz), 1.4-2.1 (complex, 4), 1.6-1.8 (complex, 3), 3.10 (m, 1), 3.54 (dd, 1, J=4, 13.5 Hz), 4.22 (q, 2, J=7 Hz), 6.20 (d, 1, J=16 Hz), 7.1-7.4 (complex, 9), 7.48 (d, 1, J=16 Hz); IR (KBr) 1705 cm^{-1}; MS (DCI) m/z 405 (base). Anal. Calcd. for $C_{25}H_{25}FN_2O_2$: C, 74.24; H, 6.23; N, 6.93. Found: C, 74.31; H, 6.09; N, 6.91.

General procedure for the preparation of 3-substituted 2-propenoates shown in Tables 10A and 10B (RS step o):

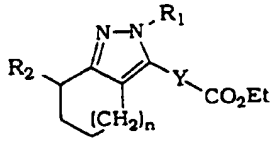
A solution of 11 mmol of triethylphosphonoacetate or triethyl phosphonopropionate in 10 mL of THF was added slowly under N_2 to a stirring suspension of 11.5 mmol of NaH in 15 mL of THF. After 45 min, the solution was cooled in an ice bath and the appropriately substituted aldehyde (10 mmol) from Table 3A, 3B, or 6 in THF (25 mL) was added dropwise. The mixture was allowed to warm to room temperature and was stirred overnight. Saturated aqueous NH_4Cl (100 mL) was added and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was crystallized or was carried on without purification.

Table 10A



Compound Number	n	R_1	R_2	mp (°C)	Mass Spectrum m/z $[M+H]^+$
197	0	4-F-Ph	H	113-114	301
198	1	4-F-Ph	(4-F-Ph)-CH_2	foam	411
199	1	4-F-Ph	c-Hex	oil	397
200	1	4-F-Ph	Et	99-100	343
201	1	4-F-Ph	Me	oil	329
202	1	4-F-Ph	Ph-CH=CH-CH_2	foam	431
203	2	(4-F-Ph)-CH_2	H	75-76	343

Table 10B



Compound Number	n	R_1	R_2	Y	mp (°C)	Mass Spectrum m/z $[M+H]^+$
204	0	4-F-Ph	H	CH=CH	94-95	301
205	1	4-F-Ph	(2-Cl-Ph)-CH_2	CH=CH	oil	439
206	1	4-F-Ph	(2-Et)Bu	CH=CH	oil	399
207	1	4-F-Ph	(2-Nap)-CH_2	CH=CH	154-155	455
208	1	4-F-Ph	(3-MeO-Ph)-CH_2	CH=CH	135-137	435
209	1	4-F-Ph	(3,4-di-MeO-Ph)-CH_2	CH=CH	foam	465
210	1	4-F-Ph	(4-Cl-Ph)-CH_2	CH=CH	oil	439
211	1	4-F-Ph	(4-F-Ph)-CH_2)	CH=CH	oil	411
212	1	4-F-Ph	(4-Me-Ph)-CH_2	CH=CH	135-136	419
213	1	4-F-Ph	(4-MeO-Ph)-CH_2	CH=CH	oil	435
214	1	4-F-Ph	(4-t-Bu-Ph)-CH_2	CH=CH	oil	461
215	1	4-F-Ph	c-Hex	CH=CH	oil	419
216	1	4-F-Ph	Et	CH=CH	oil	343
217	1	4-Cl-Ph	H	CH=CH	oil	331
218	1	4-F-Ph	H	CH=CH	76-77.5	315
219	1	4-F-Ph	H	CH=C(Me)	134-135	329
220	1	4-F-Ph	Me	CH=CH	oil	329
221	1	4-F-Ph	n-Pr	CH=CH	oil	357
222	1	4-F-Ph	Ph-$(CH_2)_2$	CH=CH	oil	419
223	1	4-F-Ph	Ph-$(CH_2)_3$	CH=CH	oil	433
224	1	4-F-Ph	Ph-CH=CH-CH_2	CH=CH	oil	431
225	1	4-F-Ph	s-Bu	CH=CH	oil	371
226	2	4-F-Ph	H	CH=CH	53-55	329
227	2	4-F-Ph-CH_2	H	CH=CH	oil	343

EXAMPLE 16

(E)-3-[2-(4-Fluorophenyl)-7-benzyl-4,5,6,7-tetrahydro-2H-indazol-3-yl]2-propen-1-ol (CP 228, RS step p):

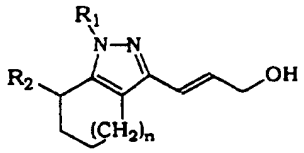
A 1.5 M solution of $(i\text{-Bu})_2AlH$ in toluene (6.53 mmol, 4.35 mL) was added under N_2 to an ice cold solution of 1.10 g (6.53 mmol) of Compound 196 in 11 mL of THF. The solution was stirred for 1.5 h and was quenched with 0.5 mL of MeOH. When the initial bubbling had ceased, 35 mL of 1 N aqueous HCl was added and the mixture was extracted with 150 mL of ether. The organic phase was washed sequentially with water, saturated aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4, the solvent was evaporated to give 0.89 g of an off-white solid. Recrystallization from EtOAc:hexanes afforded 0.62 g (63%) of the title compound as a white solid, m.p. 185-186 °C; ^1H NMR ($CDCl_3$, 300 MHz) 1.4-2.0 (complex, 5), 2.62 (m, 3), 3.05 (m, 1), 3.54 (dd, 1, J=4, 13.5 Hz), 4.27 (t, 2, J=5 Hz), 6.16 (dt, 1, J=16, 5.5 Hz), 6.43 (d, 1, J= 16 Hz), 7.1 -7.5 (complex, 9); IR (KBr) 3300, 1515 cm^{-1}; MS (DCI) m/z 363 (base), 345. Anal. Calcd. for $C_{23}H_{23}FN_2O$: C, 76.22; H, 6.40; N, 7.73. Found: C, 75.73; H, 6.01; N, 7.91.

General procedure for the preparation of 3-substituted 2-propen-1-ols shown in Tables 11A and 11B (RS step p):

A 1.5 M solution of $(i\text{-Bu})_2AlH$ in toluene (24 mmol) was added under N_2 to an ice cold solution of 10 mmol of the appropriately substituted ester from Table 10A or 10B in 50 mL of THF. The solution was stirred for 1.5

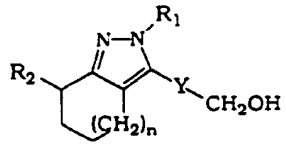
h and was quenched with 2 mL of MeOH. When the initial bubbling had ceased, 100 mL of 1 N aqueous HCl was added and the mixture was extracted with 300 mL of ether. The organic phase was washed sequentially with water, saturated aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4, the solvent was evaporated and the crude product was purified by recrystallization or MPLC.

Table 11A



Compound Number	n	R_1	R_2	mp (°C)	Mass Spectrum m/z $[M+H]^+$
229	0	4-F-Ph	H	135-136	259
230	1	4-F-Ph	(4-F-Ph)-CH_2	171-173	381
231	1	4-F-Ph	c-Hex	oil	355
232	1	4-F-Ph	Et	yellow foam	301
233	1	4-F-Ph	Me	115-116	287
234	1	4-F-Ph	Ph-CH=CH-CH_2	oil	389
235	2	(4-F-Ph)-CH_2	H	oil	301

Table 11B



Compound Number	n	R_1	R_2	Y	mp (°C)	Mass Spectrum m/z $[M+H]^+$
236	0	4-F-Ph	H	CH=CH	144-145	259
237	1	4-F-Ph	(2-Cl-Ph)-CH_2	CH=CH	177-178	397
238	1	4-F-Ph	(2-Et)Bu	CH=CH	oil	357
239	1	4-F-Ph	(2-Nap)-CH_2	CH=CH	205-207	413
240	1	4-F-Ph	(3-MeO-Ph)-CH_2	CH=CH	foam	393
241	1	4-F-Ph	(3,4-di-MeO-Ph)-CH_2	CH=CH	183-184	423
242	1	4-F-Ph	(4-Cl-Ph)-CH_2	CH=CH	204-206	397
243	1	4-F-Ph	(4-F-Ph)-CH_2	CH=CH	183-185	381
244	1	4-F-Ph	(4-Me-Ph)-CH_2	CH=CH	184-186	377
245	1	4-F-Ph	(4-MeO-Ph)-CH_2	CH=CH	172-173	393
246	1	4-F-Ph	(4-t-Bu-Ph)-CH_2	CH=CH	141-142	419
247	1	4-F-Ph	c-Hex	CH=CH	oil	355
248	1	4-F-Ph	Et	CH=CH	140-142	301
249	1	4-Cl-Ph	H	CH=CH	171-173	289
250	1	4-F-Ph	H	CH=CH	145-146	273
251	1	4-F-Ph	H	CH=C(Me)	149-150	287
252	1	4-F-Ph	Me	CH=CH	139-140	287
253	1	4-F-Ph	n-Pr	CH=CH	140-141	315
254	1	4-F-Ph	Ph-$(CH_2)_2$	CH=CH	116-118	377
255	1	4-F-Ph	Ph-$(CH_2)_3$	CH=CH	105-108	391
256	1	4-F-Ph	Ph-CH=CH-CH2	CH=CH	oil	389
257	1	4-F-Ph	s-Bu	CH=CH	oil	329
258	2	4-F-Ph	H	CH=CH	104-105	287
259	2	(4-F-Ph)-CH2	H	CH=CH	78-79	301

EXAMPLE 17

(E)-3-[2-(4-Fluorophenyl)-2,4,5,6-tetrahydrobenzo[6,7]cyclohepta-[1,2-c]pyrazol-3-yl]-2-propen-1-ol (CP 260, RS step q):

1-Benzosuberone (25 mmol, 4.10 g, 3.74 mL) was added dropwise under N_2 to a stirring suspension of 4.23 g (26 mmol) of 4-fluorophenyl-hydrazine · HCl and 2.13 g (26 mmol) of NaOAc in 15 mL of absolute EtOH. The mixture was refluxed for 3 h and allowed to stir at room temperature overnight. After concentration, the residue was partitioned between water and Et_2O. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give 6.68 g of crude hydrazone as an orange solid. The crude product was dissolved in 25 mL of THF and added dropwise under N_2 to a solution of LDA (made by adding 7.34 mL (52.3 mmol, 5.29 g) of diisopropylamine in 20 mL of THF to 33.7 mL (52.3 mmol) of 1.6 M *n*-BuLi in hexanes) at -10°C. The resulting dark brown solution was stirred for 30 min and was treated with a solution of methyl 4-tetrahydropyranyloxy-2-butenoate (Harnish, W.; Morera, E.; Ortar, G. J. Org. Chem., 1985, 50, 1990-2) in 5 mL of THF. After 1.5 h, 42 mL of 3 N aqueous HCl was added to the cold solution, which was then refluxed for 15 min. Et_2O (150 mL) was added and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine. After drying over Na_2SO_4, the mixture was concentrated to give 12 g of light brown oil. The crude residue was refluxed under N_2 for 8 h with 0.31 g (1.25 mmol) of pyrdinium *p*-toluenesulfonate in 50 mL of MeOH. The solution was concentrated and the residue was partitioned between Et_2O and water. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give 9.2 g of brown oil. Purification by MPLC using 1:3 EtOAc:hexanes afforded 3.35 g of yellow solid which was

recrystallized from EtOAc:hexanes to give 3.00 g (36%) of the title compound as a white solid, m.p. 127-128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 2.15 (m, 2), 2.84 (m, 4), 4.30 (m, 2), 6.16 (dt, 1, J= 16, 5 Hz), 6. 44 (d, 1, J= 16 Hz), 7.2 (complex, 5), 7.50 (m, 2), 8.07 (m, 1); IR (KBr) 3300 (broad), 1515, 1223 cm^{-1}; MS (DCI) m/z 335 (base), 317. Anal. Calcd. for $C_{21}H_{19}FN_2O$: C, 75.43; H, 5.73; N, 8.38. Found: C, 75.26; H, 5.52; N, 8.24.

EXAMPLE 18

(E)-3-[4,5-Dihydro-2-(4-fluorophenyl)-2H-benz[g]indazol-3-yl]-2-propen-1-ol (CP 261, RS step q):

α-Tetralone (25 mmol, 3.65 g, 3.33 mL) was added dropwise under N_2 to a stirring suspension of 4.23 g (26 mmol) of 4-fluorophenylhydrazine · HCl and 2.13 g (26 mmol) of NaOAc in 15 mL of absolute EtOH. The mixture was refluxed for 2 h, cooled, and concentrated to remove the solvent. The residue was partitioned between water and Et_2O. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give 6.21 g of crude hydrazone as a yellow solid. The crude product was dissolved in 30 mL of THF and added dropwise under N_2 to a solution of LDA (made by adding 7.18 mL (51.2 mmol, 5.18 g) of diisopropylamine in 10 mL of THF to 33.0 mL (51.2 mmol) of 1.55 M *n*-BuLi in hexanes) at -10°C. The resulting dark brown solution was stirred for 30 min and was treated with a solution of methyl 4-tetrahydropyranyloxy-2-butenoate (Harnish, W.; Morera, E.; Ortar, G. J. Org. Chem., 1985, 50, 1990-2) in 15 mL of THF. After 1.5 h, 42 mL of 3 N aqueous HCl was added to the cold solution, which was then refluxed for 1 h. Et_2O (150 mL) was added and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine. After drying over Na_2SO_4, the mixture was concentrated to give 10.2 g of a light brown oil. The crude residue was refluxed under N_2 for 8 h with 0.31 g (1.25 mmol) of pyrdinium *p*-toluenesulfonate in 50 mL of MeOH. The solution was concentrated and the residue was partitioned between Et_2O and water. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give 8.44 g of a brown oil. Purification by MPLC using 1:3 EtOAc:hexanes afforded 3.03 g of an off-white solid which was recrystallized from EtOAc:hexanes to give 2.37 g (37%) of the title compound as an off-white solid, m.p. 149-150°C; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.70 (t, 1, J=6 Hz), 2.91 (m, 2), 3.02 (m, 2), 4.31 (dt, 2, J=1.5, 4.5 Hz), 6.21 (dt, 1, J=16, 5 Hz), 6.46 (dd, 1, J=1.5, 16 Hz), 7.18 (t, 2, J=8.5 Hz), 7.25 (m, 3), 7.48 (dd, 2, J=5, 8.5 Hz), 7.92 (m, 1); IR (KBr) 3300 (broad), 1509, 1221 cm^{-1}; MS (DCI) m/z 321 (base), 303. Anal. Calcd. for $C_{20}H_{17}FN_2O$: C, 74.98; H, 5.35; N, 8.74. Found: C, 74.78; H, 5.33; N, 8.97.

EXAMPLE 19

(E)-3-[2-(4-Fluorophenyl)-7-benzyl-4,5,6,7-tetrahydro-2H-indazol-3-yl]-2-propenal (CP 262, RS step r):

MnO_2 (30 mmol, 2.20 g) was added in one portion to a stirring suspension of 0.84 g (2.32 mmol) of Compound 228 in 15 mL of benzene. The mixture was refluxed gently under N_2 for 3 h. After cooling, the slurry was filtered through a Celite pad and the solids were washed with 100 mL of CH_2Cl_2. The filtrate was concentrated to give 0.75 g of a yellow solid which was purified by MPLC (1:8 EtOAc:hexanes) to provide 0.529 g (63%) of the title compound as a pale yellow solid, m.p. 130-131°C; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.6-2.1 (complex, 4), 2.6-2.8 (complex, 3), 3.10 (m, 1), 3.54 (dd, 1, J=4, 13.5 Hz), 6.48 (dd, 1, J=7.5, 16 Hz), 7.1-7.5 (complex, 10), 9.52 (d, 1, J=7.5 Hz); IR (KBr) 1677, 1617, 1512 cm^{-1}; MS (DCI) m/z 361 (base), 307, 269, 241, 178. Anal. Calcd. for $C_{23}H_{21}FN_2O$: C, 76.65; H, 5.87; N, 7.77. Found: C, 76.47; H, 5.61; N, 7.35.

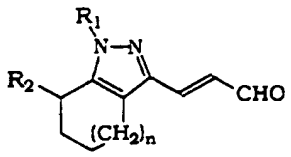
General procedure for the preparation of 3-substituted 2-propenals shown in Tables 12A and 12B. RS step r:

Method A: MnO_2 (100-120 mmol) was added in one portion to a stirring suspension of 10 mmol of the appropriately substituted alcohol from Table 11A or 11B or Example 17 or 18 in benzene (60 mL). The mixture was refluxed gently under N_2 until TLC analysis indicated that the starting material was completely consumed. After cooling, the slurry was filtered through a Celite pad and the black solids were washed with 250 mL of CH_2Cl_2. The filtrate was concentrated and the crude product was purified by MPLC or recrystallization.

Method B: CrO_3 (60 mmol) was added under N_2 in several portions to an ice-cold solution of 120 mmol of pyridine in 100 mL of CH_2Cl_2. The mixture was stirred at room temperature for 15 min and was re-cooled to 0°C. The appropriately substituted alcohol from Table 11A or 11B was either dissolved in a minimum amount of CH_2Cl_2 and added dropwise or, if solid, was added in 5-10 portions over a 30 min period. The slurry was stirred 30-45 min at 0°C and was allowed to stir at room temperature until TLC analysis indicated the reaction was complete. Et_2O (200 mL) was added and the solvent was decanted from the tarry residue through a Celite

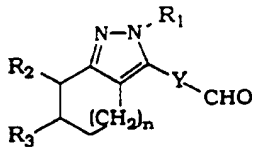
pad. The residue was sonicated with two 100 mL portions of Et_2O, which were also decanted through Celite. The combined filtrates were washed successively with 100 mL of 1 N aqueous HCl, 100 mL of water, two 100 mL portions of saturated aqueous $NaHCO_3$, and brine. The ethereal solution was dried (Na_2SO_4), concentrated, and purified by MPLC or recrystallization.

Table 12A



Compound Number	Method	n	R_1	R_2	mp (°C)	Mass Spectrum m/z $[M+H]^+$
263	B	0	4-F-Ph	H	138-139	257
264	A	1	4-F-Ph	(4-F-Ph)-CH_2	133-136	379
265	A	1	4-F-Ph	c-Hex	foam	353
266	A	1	4-F-Ph	Et	118-121	299
267	A	1	4-F-Ph	Me	oil	285
268	A	1	4-F-Ph	Ph-CH=CH-CH_2	foam	387
269	A	2	(4-F-Ph)-CH_2	H	oil	299

Table 12B



Compound Number	Method	n	R_1	R_2	R_3	Y	mp (°C)	Mass Spectrum m/z $[M+H]^+$
270	B	0	4-F-Ph	H	H	CH=CH	127-128	257
271	A	1	4-F-Ph	(2-Cl-Ph)-CH_2	H	CH=CH	184-185	395
272	A	1	4-F-Ph	(2-Et)Bu	H	CH=CH	98-100	355
273	A	1	4-F-Ph	(2-Nap)-CH_2	H	CH=CH	174-175	411
274	A	1	4-F-Ph	(3-MeO-Ph)-CH_2	H	CH=CH	97-99	391
275	A	1	4-F-Ph	(3,4-di-MeO-Ph)-CH_2	H	CH=CH	foam	421
276	A	1	4-F-Ph	(4-Cl-Ph)-CH_2	H	CH=CH	144-145	395
277	A	1	4-F-Ph	(4-F-Ph)-CH_2	H	CH=CH	oil	379
278	A	1	4-F-Ph	(4-Me-Ph)-CH_2	H	CH=CH	160-162	375
279	A	1	4-F-Ph	(4-MeO-Ph)-CH_2	H	CH=CH	141-142	391
280	A	1	4-F-Ph	(4-t-Bu-Ph)-CH_2	H	CH=CH	145-148	417
281	A	1	4-F-Ph	------6,7-Benzo------		CH=CH	foam	319
282	A	1	4-F-Ph	c-Hex	H	CH=CH	oil	353
283	A	1	4-F-Ph	Et	H	CH=CH	99-101	299
284	B	1	4-Cl-Ph	H	H	CH=CH	133-134	287
285	B	1	4-F-Ph	H	H	CH=CH	122-123	271
286	A	1	4-F-Ph	H	H	CH=C(Me)	172-173	285
287	A	1	4-F-Ph	Me	H	CH=CH	145-146	285
288	A	1	4-F-Ph	n-Pr	H	CH=CH	92-93	313
289	A	1	4-F-Ph	Ph-$(CH_2)_2$	H	CH=CH	132-134	375
290	A	1	4-F-Ph	Ph-$(CH_2)_3$	H	CH=CH	oil	389
291	A	1	4-F-Ph	Ph-CH=CH-CH_2	H	CH=CH	foam	387
292	A	1	4-F-Ph	s-Bu	H	CH=CH	oil	327
293	A	2	4-F-Ph	------7,8-Benzo------		CH=CH	208-210	333
294	A	2	4-F-Ph	H	H	CH=CH	92-93	285
295	A	2	(4-F-Ph)-CH_2	H	H	CH=CH	oil	299

EXAMPLE 20

Ethyl (E)-(3RS,5SR)-7-[7-benzyl-2-(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]-3,5-dihydroxy-6-heptenoate (CP 47, RS step s):

A solution of 1.11 mL of ethyl acetoacetate (8.72 mmol, 1.13 g) in 10 mL of THF was added dropwise under N_2 to a stirring suspension of 0.220 g (9.16 mmol) of oil-free NaH in 10 mL of THF. The mixture was stirred for 30 min and cooled to -10°C in an ice/acetone bath. *n*-BuLi in hexanes (1.6 M, 8.72 mmol, 5.45 mL) was added slowly, producing a pale yellow solution. After 30 min, a solution of 2.86 g (7.93 mmol) of Compound 262 in 25 mL of THF was added and the resulting yellow solution was stirred for 45 min. Saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with 100 mL of Et_2O. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated to give 3.84 g of crude hydroxy keto ester as an orange oil.

The crude intermediate was dissolved in 8 mL of MeOH and 25 mL of THF. A 1.0 M solution of Et_3B in THF (8.60 mmol, 8.60 mL) was added and 20 mL of air was bubbled into the solution *via* syringe. The solution was stirred under N_2 for 2 h and was cooled to -78 °C. $NaBH_4$ (8.60 mmol, 0.33 g) was added in one portion. The mixture was allowed to warm slowly to room temperature and was stirred overnight. Saturated aqueous NH_4Cl (100 mL) was added and the mixture was extracted with 150 mL of Et_2O. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated to give an oil which was dissolved in 50 mL of MeOH and stirred vigorously under air overnight. The solution was concentrated to give 3.86 g of a yellow oil. Purification by MPLC using 2:3 EtOAc:hexanes yielded 1.83 g (47%) of the title compound as a white foam; ^1H NMR ($CDCl_3$,

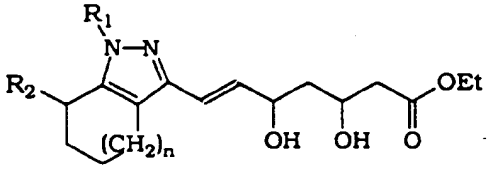
300 MHz) 1.27 (t, 3, J=7 Hz), 1.3-2.0 (complex, 6), 2.48 (d, 2, J=6 Hz), 2.60 (m, 3), 3.03 (m, 1), 3.55 (m, 1), 3.63 (s, 1), 3.78 (s, 1), 4.17 (q, 2, J=7 Hz), 4.30 (m, 1), 4.50 (m, 1), 6.00 (dd, 1, J=6, 16 Hz), 6.44 (d, 1, J=16 Hz), 7.1-7.5 (complex, 9); ^{13}C NMR ($CDCl_3$, 75 MHz) 14.2, 21.6, 22.8, 27.8, 36.2, 40.7, 41.5, 42.7, 60.9, 68.4, 72.5, 115.7, 116.0 (J_{C-F} = 23 Hz), 117.9, 125.9, 127.3 (J_{C-F} = 8 Hz), 128.2, 129.3, 135.0, 135.4, 136.2, 140.6, 153.3, 161.8 (J_{C-F} = 247 Hz), 172.5; IR (KBr) 3400 (broad), 1732, 1514 cm^{-1}; MS (DCI) m/z 493, 457, 401, 333, 241, 91 (base). Anal. Calcd. for $C_{29}H_{33}FN_2O_4$: C, 70.71; H, 6.75; N, 5.69. Found: C, 70.90; H, 7.04; N, 5.67.

General procedure for the preparation of 7-substituted (E)-(3RS,5SR)-3,5-dihydroxy-6-heptenoates shown in Tables 13A and 13B (RS step s):

A solution of 11 mmol of ethyl acetoacetate in 10 mL of THF was added dropwise under N_2 to a stirring suspension of 11.5 mmol of oil-free NaH in 15 mL of THF. The mixture was stirred for 30 min and cooled to -10°C in an ice/acetone bath. *n*-BuLi in hexanes (11 mmol of a 1.6 M solution) was added slowly, producing a pale yellow solution. After 30 min, a solution of 10 mmol of the appropriately substituted aldehyde from Table 12A or 12B in 30 mL of THF was added and the resulting yellow solution was stirred for about 1 h. Saturated aqueous NH_4Cl (75 mL) was added and the mixture was extracted with 150 mL of Et_2O. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated to give the crude hydroxy keto ester which was carried on without purification.

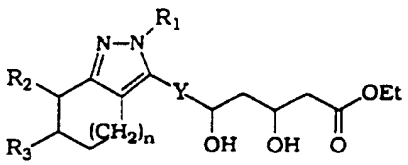
The crude intermediate was dissolved in 10 mL of MeOH and 30 mL of THF. A 1.0 M solution of Et_3B in THF (11 mmol) was added and 20 mL of air was bubbled into the solution via syringe. The solution was stirred under N_2 for 2 h and was cooled to -78 °C. $NaBH_4$ (11 mmol) was added in one portion, causing some gas evolution. The mixture was allowed to warm slowly to room temperature and was stirred overnight. Saturated aqueous NH_4Cl (150 mL) was added and the mixture was extracted with 200 mL of Et_2O. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated. The residue, which smelled of excess Et_3B, was then dissolved in MeOH and stirred vigorously under air until TLC analysis showed complete conversion of the boron intermediates to the desired product (4-24 h). The MeOH was removed by rotary evaporation and the crude material was purified by MPLC.

Table 13A



Compound Number	n	R_1	R_2	Mass Spectrum m/z $[M+H]^+$
48	0	4-F-Ph	H	389
49	1	4-F-Ph	(4-F-Ph)-CH_2	511
50	1	4-F-Ph	c-Hex	485
51	1	4-F-Ph	Et	431
52	1	4-F-Ph	Me	417
53	1	4-F-Ph	Ph-CH=CH-CH_2	515
54	2	(4-F-Ph)-CH_2	H	431

Table 13B



Compound Number	n	R_1	R_2	R_3	Y	Mass Spectrum m/z $[M+H]^+$
55	0	4-F-Ph	H	H	CH=CH	389
56	1	4-F-Ph	(2-Cl-Ph)-CH_2	H	CH=CH	528
57	1	4-F-Ph	(2-Et)Bu	H	CH=CH	487
58	1	4-F-Ph	(3-MeO-Ph)-CH_2	H	CH=CH	523
59	1	4-F-Ph	(3,4-di-MeO-Ph)-CH_2	H	CH=CH	553
60	1	4-F-Ph	(4-Cl-Ph)-CH_2	H	CH=CH	528
61	1	4-F-Ph	(4-F-Ph)-CH_2	H	CH=CH	511
62	1	4-F-Ph	(4-Me-Ph)-CH_2	H	CH=CH	507
63	1	4-F-Ph	(4-MeO-Ph)-CH_2	H	CH=CH	523
64	1	4-F-Ph	(4-t-Bu-Ph)-CH_2	H	CH=CH	549
65	1	4-F-Ph	------6,7-Benzo------		CH=CH	451
66	1	4-F-Ph	c-Hex	H	CH=CH	485
67	1	4-F-Ph	Et	H	CH=CH	431
68	1	4-Cl-Ph	H	H	CH=CH	419
69	1	4-F-Ph	H	H	CH=CH	403
70	1	4-F-Ph	H	H	CH=CMe	417
71	1	4-F-Ph	Me	H	CH=CH	417
72	1	4-F-Ph	n-Pr	H	CH=CH	445
73	1	4-F-Ph	Ph-$(CH_2)_2$	H	CH=CH	507
74	1	4-F-Ph	Ph-$(CH_2)_3$	H	CH=CH	521
75	1	4-F-Ph	s-Bu	H	CH=CH	459
76	2	4-F-Ph	------7,8-Benzo------		CH=CH	465
77	2	4-F-Ph	H	H	CH=CH	417
78	2	(4-F-Ph)-CH_2	H	H	CH=CH	431

EXAMPLE 21

(E)-(4RS,6SR)-6-[2-[7-Benzyl-2-(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]ethenyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (CP 79, RS step w):

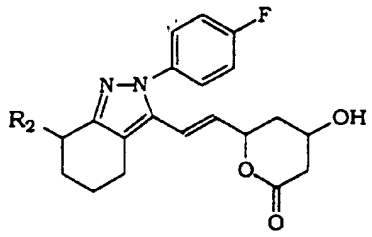
A 5.0 mL (1.25 mmol) portion of 0.25 N aqueous NaOH was added slowly to an ice-cold solution of 0.500 g (1.02 mmol) of Compound 47 in 15 mL of methanol. After 15 min, the solution was allowed to warm to room temperature and was stirred for 1 h. The solution was concentrated to dryness using a rotary evaporator and was mixed with 50 mL of water and 100 mL of CH_2Cl_2. The mixture was acidified to pH 2-3 with aqueous 1 N HCl. The aqueous layer was extracted with 50 mL of CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude dihydroxy acid (0.49 g) was dissolved in 12 mL of CH_2Cl_2 and cooled in an ice bath. 1-Cyclohexyl-3- (2-morpholinoethyl)-carbodiimide metho-*p*-toluenesulfonate (1.07 mmol, 0.455 g) was added in one portion and the mixture was allowed to warm slowly to room temperature and was stirred overnight. EtOAc (100 mL) was added and the white solids were removed by suction filtration. The solids were washed with more EtOAc and the combined filtrates were washed with water and brine and dried (Na_2SO_4). The solution was concentrated to give 0.60 g of crude product which was purified by MPLC (1:1 EtOAc:hexanes) to provide 0.29 g (64%) of the title compound as a white solid, m.p. 185-187 °C; ^1H NMR ($CDCl_3$, 300 MHz) 1.4-2.1 (complex, 6), 2.21 (d, 1, J=2.5 Hz), 2.62 (m, 4), 2.74 (dd, 1, J=4.5, 18 Hz), 3.06 (m, 1), 3.53 (dt, 1, J=13.5, 3.5), 4.40 (m, 1), 5.25 (m, 1), 6.01 (dd, 1, J=6.5, 16 Hz), 6.49 (d, 1, J=16 Hz), 7.1 -7.5 (complex, 9); IR (KBr) 3300 (broad), 1741, 1513 cm^{-1}; MS (DCI) m/z 447, 429, 385 (base), 359.

Anal. Calcd. for $C_{27}H_{27}FN_2O_3$: C, 72.63; H, 6.09; N, 6.27. Found: C, 72.61; H, 6.10; N, 5.97.

General procedure for the preparation of 6-substituted (E)-(4RS,6SR)-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-ones shown in Table 14, RS step w:

A 5.0 mL (1.25 mmol) portion of 0.25 N aqueous NaOH was added slowly to an ice-cold solution of 1.02 mmol of the appropriately substituted ester from Table 8, 13A, or 13B in methanol (15 mL). After 15 min, the solution was allowed to warm to room temperature and was stirred for 1 h. The solution was concentrated to dryness using a rotary evaporator and was mixedwith 50 mL of water and 100 mL of CH_2Cl_2. The mixture was acidified to pH 2-3with aqueous 1 N HCl. The aqueous layer was extracted with 50 mL of CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude dihydroxy acid was dissolved in 12 mL of CH_2Cl_2 and cooled in an ice bath. 1-Cyclohexyl-3-(2-morpholinoethyl) carbodiimide metho-*p*-toluenesulfonate (1.1 mmol) was added in one portion and the mixture was allowed to warm slowly to room temperature and was stirred overnight. EtOAc (100 mL) was added and the white solids were removed by suction filtration. The solids were washed with more EtOAc and the combined filtrates were washed with water and brine and dried (Na_2SO_4). The solution was concentrated and the crude product was purified by MPLC.

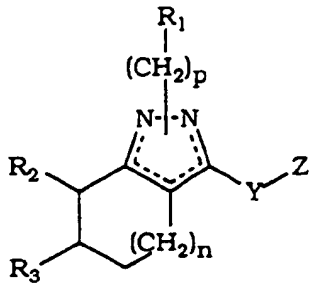
Table 14



Compound Number	R_2	mp (°C)	Mass Spectrum m/z $[M+H]^+$
80	(2-Et)Bu	foam	441
81	(2-Nap)-CH_2	foam	497
82	(4-t-Bu-Ph)-CH_2	foam	503
83	H	foam	357

Claims

1. A compound of the formula I:



I

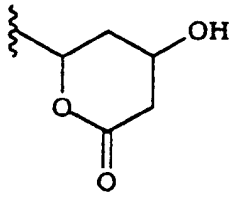
wherein R_1 is selected from any one of H, alkyl, aryl, or substituted aryl; wherein R_2 is selected from any one of H, alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, aralkenyl, or cycloalkyl;

wherein R_3 is H; or

wherein R_2 and R_3 may be taken together to form a benzo or naphtho ring system;

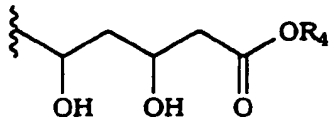
wherein Y is is alkyl or alkenyl;

wherein Z is selected from any one of:



II

or

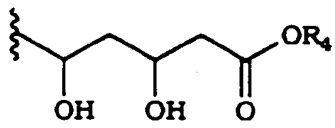


III

wherein R_4 is selected from anyone of H, alkyl, a protonated amine of the formula $HN(R_6)_3$+ wherein R_5 is any one of H or alkyl, or cation;

wherein n = 0 to 3 and p = 0 to 3 and pharmaceutically acceptable acid salts thereof.

2. The compound of claim 1, wherein R_1 is a substituted aryl, Y is CH=CH, n = 1; p = 0 and z is



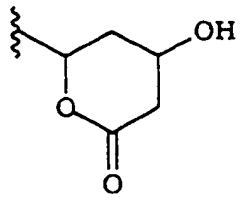
3. The compound of claim 2, wherein R_1 is substituted with a halogen.

4. The compound of claim 3, wherein the halogen is fluoro.

5. The compound of claim 4, wherein R_4 is a cation.

6. The compound of claim 5, wherein the cation is selected from any one of Na^+, K^+, Li^+, Ca^{+2}, or Mg^{+2}.

7. The compound of claim 1, wherein R_1 is a substituted aryl, Y is CH=CH, n = 1, p = 0 and Z is



II

8. The compound of claim 7, wherein R_1 is substituted with a halogen.

9. The compound of claim 8, wherein the halogen is fluoro.

10. The compound of claim 1, wherein the compound is (E)-(3RS,5SR)-7-[7-[(1,1'-biphenyl-4-yl)methyl]-2-(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]-3,5-dihydroxy-6-heptenoic acid · sodium salt.

11. The compound of claim 1, wherein the compound is (E)-(3RS,5SR)-7-[2- (4-fluorophenyl)-7-[(2-naphthyl)methyl]-4,5,6,7-tetrahydro-2H-indazol-3-yl]-3,5-dihydro-6-heptenoic acid · sodium salt.

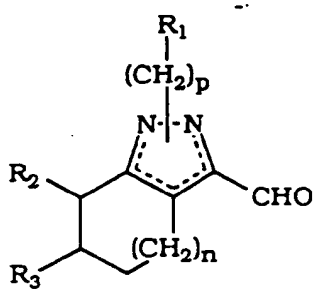
12. The compound of claim 1, wherein the compound is (E)-(3RS,5SR)-7-[7-(4-*t*-butylbenzyl)-2-(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]3,5-dihydroxy-6-heptenoic acid · sodium salt.

13. The compound of claim 1, wherein the compound is (E)-(4RS,6SR)-6-[2-[7-(4-*t*-butylbenzyl)-2-(4-fluorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]ethenyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one.

14. A pharmaceutical composition comprising the compound of any one of claims 1 to 13 in combination with a pharmaceutically acceptable carrier, said compound being present in an amount sufficient to inhibit cholesterol biosynthesis.

15. The compound of any one of claims 1 to 13 or the composition of claim 14 for use in inhibiting cholesterol biosynthesis.

16. A compound of the formula X:



X

wherein R_1 is selected from any one of H, alkyl, aryl, or substituted aryl; wherein R_2 is selected from any one of alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, aralkenyl, or cycloalkyl;
wherein R_3 is H; or
wherein R_2 and R_3 may be taken together to form a benzo or naphtho ring system;
wherein n = 0 to 3 and p = 0 to 3 and pharmaceutically acceptable acid salts thereof.

17. A process for the synthesis of the compound of any one of claims 1 to 13 substantially as described with reference to the Reaction Scheme set out in the description.

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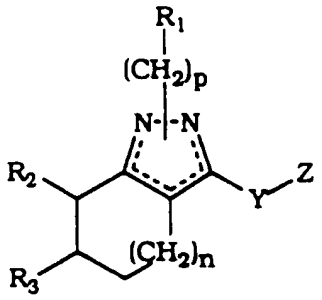
(54) **Tetrahydroindazole, tetrahydrocyclopentapyrazole, and hexahydrocycloheptapyrazole compounds and their use as HMG-COA reductase inhibitors.**

(57) Compounds of the general formula I :



are disclosed as useful in the treatment or prevention of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis. Novel intermediate compounds used to make the compound of formula I are also disclosed.

EP 0 529 854 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 92 30 7264.9

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	WO-A-8 600 307 (SANDOZ S.A.)		C07D231/54 A61K31/415 C07D231/56 C07D405/06 A61K31/35
D,A	WO-A-8 607 357 (THE UPJOHN COMPANY)		
D,A	US-A-4 613 610 (SANDOZ PHARMACEUTICALS CORP.)		
D,A	EP-A-0 287 890 (BAYER AKTIENGESELLSCHAFT)		
D,A	WO-A-8 806 584 (BRISTOL-MYERS COMPANY) & GB-A-2 202 846		
D,A	US-A-4 761 419 (WARNER-LAMBERT COMPANY)		
D,A	US-A-4 739 073 (SANDOZ PHARMACEUTICALS)		
D,A	US-A-4 808 607 (SANDOZ PHARMACEUTICALS CORP.)		
D,A	US-A-4 822 799 (SANDOZ PHARMACEUTICALS CORP.)		
D,A	US-A-4 868 185 (WARNER-LAMBERT COMPANY)		TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07D A61K
D,A	TETRAHEDRON LETTERS. vol. 29, no. 8, 1988, OXFORD GB pages 929 - 930 E.BAADER,A.O. 'SYNTHESIS OF A NOVEL HMG-COA REDUCTASE INHIBITOR'		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	02 DECEMBER 1992	DE BUYSER I.A.F.

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